A.M.A. Archives OF INTERNAL MEDICINE

AUGUST 1956

VOLUME 98 NUMBER 2

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Rheumatic Fever
Gene H. Stollerman, Chicago

The Manifestations and Treatment of Poisoning Due to Nerve Gas and Other Organic Phosphate Anticholinesterase Compounds
David Grob, Baltimore

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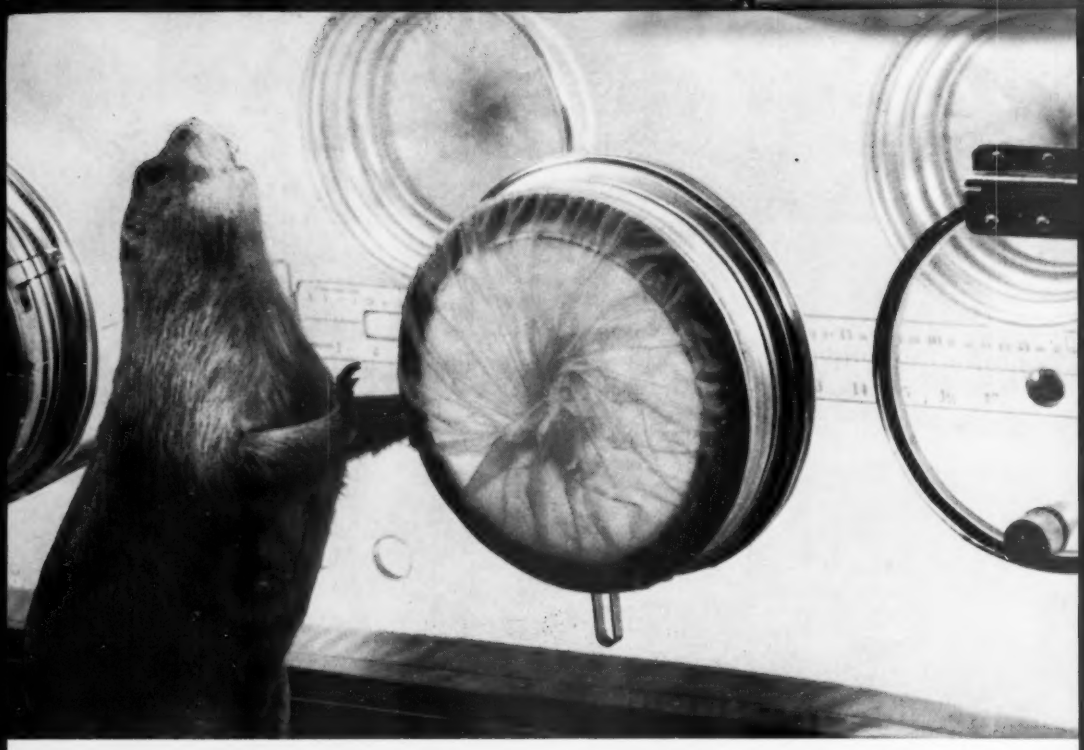

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References: 1. Hisaw, F. L.: Physiol. Zoöl. *2*:59 (Jan.) 1929. 2. Hisaw, F. L.; Meyer, R. K., and Fevold, H. L.: Proc. Soc. Exper. Biol. & Med. *27*:400 (Feb.) 1930. 3. Hisaw, F. L., and Zarrow, M. X.: Vitamins & Hormones *8*:151, 1951. 4. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. & Metab. *14*:531 (May) 1954. 5. Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. & Metab. *15*:206 (Jan.) 1955. 6. Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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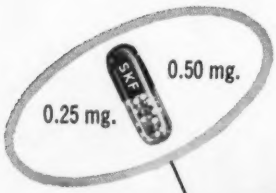

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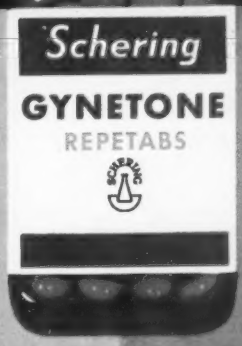

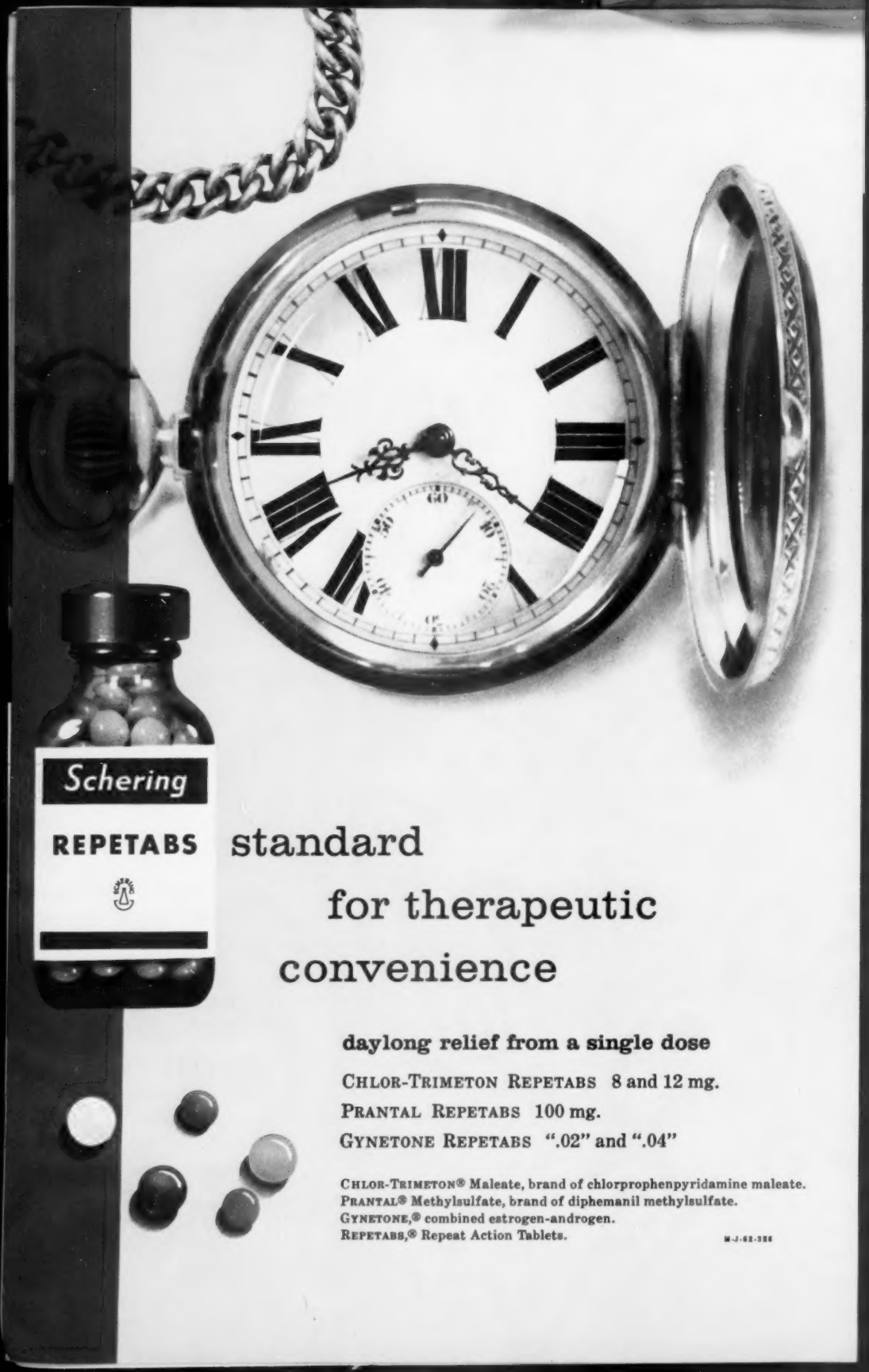

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(1) Clara, M.: Med. Monatsschr. 7:356, 1953. (2) Brauer, R. W., and Pessotti, R. L.: Science *115*:142, 1952. (3) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

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2. Kelly, H. T.: Impact of Modern Nutrition on Twentieth Century Morbidity, Pennsylvania M. J. 58: 481 (May) 1955.
3. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 5, Philadelphia, W. B. Saunders Company, 1955, pp. 139, 140.

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The Association of Smoking with Cancer of the Urinary Bladder in Humans

ABRAHAM M. LILIENFELD, M.D., M.P.H., Buffalo
MORTON L. LEVIN, M.D., Albany, N. Y.
and
GEORGE E. MOORE, M.D., Ph.D., Buffalo

Recently, in an experiment designed to study the effects of the intraoral application of tobacco tar as a carcinogenic agent in mice, Holsti and Ermala observed that about 75% of the mice developed urinary bladder papillomas in contrast to none of the control group and that 10% of the experimental group had papillomas that were histologically malignant.[1] It would be of considerable interest to determine if in humans a similar relationship exists. As a first approach to the study of such a relationship, the clinical records of patients admitted to the Roswell Park Memorial Institute were reviewed. This is a report of the results of this analysis.

Method of Study

The method of study consisted of a comparison of the histories of tobacco use of a group of patients with urinary bladder cancer with those of patients with other cancers and noncancerous conditions. The other cancers selected for study were cancer of the prostate in the case of men and cancer of the breast in women. The noncancerous conditions consisted of the following two groups: (1) benign lesions of the bladder, composed of cystitis, vesical calculi, diverticulum, etc., and (2) a group of patients referred to the Institute with a suspicious diagnosis of cancer because of the presence of various symptoms, but no specific disease or pathological process found by various diagnostic tests. This latter group will be referred to as the "no disease" group in this report. In view of the previous studies concerning the association of lung cancer with cigarette smoking, we considered it of interest to include men with lung cancer in our comparisons. The number of women with lung cancer was not sufficient for analysis.

The records of all patients with the above diagnoses who were admitted to the Roswell Park Memorial Institute from 1945 to 1955 were reviewed. Since the number of nonwhite patients was so few, these were omitted from the analysis. A few patients with cancers of other sites in addition to the sites studied were also omitted in order to eliminate any confusing factors. In addition, the analysis was limited to patients 45 years of age and over, since the preponderance of cancer patients were in this general age group.

For each patient the following information was obtained from the record: age at diagnosis, history of tobacco use including type of tobacco used, and number of years during which each type was used. This information had been originally obtained from the patient at the time of the first visit to the Institute by a group of interviewers whose sole duty it was to interview all admitted patients prior to the physician's examination and the establishment of a definite diagnosis. In a small percentage of cases, the diagnosis may have been apparent to the interviewer, since patients treated prior to admission were admitted for recurrences or special

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therapy. Even in such instances, the nature of the procedure was such that the chances for interviewer bias were practically negligible. In the tables presented in this report the number of patients may differ due to varying but small numbers of patients on whom information was not available for certain characteristics.

Results

Frequency of Tobacco Use.—The categories of tobacco use whose frequencies were analyzed were as follows: (1) any type of tobacco, (2) cigarettes only, (3) cigarettes alone and in combination with other types, and (4) all other types of tobacco besides cigarettes. The over-all frequencies of men in these different categories of tobacco use by class of patient are presented in the upper half of Table 1. Because of variations in the age distribution of patients in the different classes, the frequencies were adjusted for age by the usual method employed in vital statistics practice, using the age distribution of all of the men as the standard population. These age-adjusted frequencies are presented in the lower half of Table 1.

TABLE 1.—*Percentage of Men Aged Forty-Five Years and Over with History of Tobacco Use, by Class of Patient*

Class of Patient	No. of Patients	Per Cent Tobacco Users			
		Any Type of Tobacco	Cigarettes Only	Cigarettes Alone and in Combination with Other Types of Tobacco	Any Type Other than Cigarettes
		Unadjusted percentage			
Bladder cancer	321	84.1	47.0	59.8	24.3
Benign bladder conditions	39	76.9	30.8	38.4	38.5
No disease	337	70.9	40.0	46.3	24.6
Prostate cancer	287	74.6	28.2	37.2	37.3
Lung cancer	306	91.8	67.3	84.3	7.5
		Age-Adjusted Percentage			
Bladder cancer	321	84.7	48.7	61.4	23.2
Benign bladder conditions	39	77.9	32.8	37.1	40.8
No disease	337	70.8	35.8	44.1	26.7
Prostate cancer	287	77.8	32.6	42.3	36.1
Lung cancer	306	92.0	64.9	82.9	9.1

From Table 1 we note that 84.7% of men with urinary bladder cancer used any type of tobacco, as compared with 70.8% to 77.8% of patients with benign bladder tumors, prostate cancer, and no disease. The frequency for the lung-cancer group is 91.5%. Limiting our consideration to the use of cigarettes, we note that the frequencies of cigarette use, either alone or in combination with other types of tobacco, is higher among bladder- and lung-cancer patients than among the other groups. However, the use of other types of tobacco is no greater among bladder-cancer patients than in the no-disease group, although it is more frequent among prostate-cancer patients than among the no-disease group.

For determining whether these differences in percentages are statistically significant, a method proposed by Cochran has been used.[2] This method consists of determining the differences in age-specific frequencies of tobacco use between the two classes of patients being compared. These age-specific differences are then weighted by a combination of the numbers of patients upon which the frequencies are based. A

weighted mean difference and its standard error are then obtained for the over-all comparison of the two patient classes. The probability of having obtained such a weighted mean difference is determined from tables of the normal distribution. The weighted mean differences, their standard errors, and probability levels for various comparisons are presented in Table 2.

other types of tobacco is significantly less in the bladder-cancer than in the prostate-cancer group.

From Table 1, it is apparent that a larger proportion of patients with prostate cancer used any type of tobacco and all other types besides cigarettes than did those in the no-disease group. However, as is indicated in Table 2, these differences are not statistically

TABLE 2.—*Comparison of Selected Classes of Men with Regard to per Cent of Tobacco Use*

Classes of Patients Being Compared	Any Type of Tobacco			Cigarettes Only			Cigarettes Alone and in Combination with Other Types of Tobacco			Any Type Other Than Cigarettes		
	Weighted Mean Difference %	S.E.*	P†	Weighted Mean Difference %	S.E.*	P†	Weighted Mean Difference, %	S.E.*	P†	Weighted Mean Difference, %	S.E.*	P†
Bladder cancer and prostate cancer	+8.45	3.28	0.01	+15.7	3.81	<0.001	+19.6	3.92	<0.001	−11.3	3.75	<0.01
Bladder cancer and no disease	+13.8	3.31	<0.001	+13.1	3.79	<0.001	+17.3	3.86	<0.001	− 3.5	3.34	0.30
Prostate cancer and no disease	+4.59	3.79	0.20	----	----	----	----	----	----	+ 7.2	3.82	>0.05

* S. E. indicates standard error of weighted mean difference.
†P indicates Probability that this difference could have arisen by chance alone.

We note that a comparison of the bladder-cancer and the no-disease groups indicates that the frequency of use of cigarettes, either alone or in combination with other types of tobacco, was higher in the bladder-cancer group than in the no-disease group; these differences are statistically significant at probability levels of less than 0.001. The difference in the frequencies of use of all other types of tobacco in the bladder-cancer and the no-disease group is not statistically significant. (In this report, differences will be considered statistically significant at probability levels of 0.05 or less). The results of the comparison of the frequencies in the bladder-cancer group with those in the prostate-cancer group are similar to that obtained in the comparison of the bladder-cancer and the no-disease groups, with the exception that the frequency of use of all

significant. No statistical tests were carried out with regard to lung cancer, since it is clear from the degree of the differences and from the results of our previous analyses that they are statistically significant.

A similar analysis was carried out for women with bladder cancer. In this instance, the only type of tobacco used was cigarettes. The percentages of cigarette-smokers among women by class of patients are presented in Table 3. We note that the unadjusted percentage of cigarette smokers among bladder-cancer patients is less than in the other classes of patients. However, after age adjustment, the percentage of cigarette smokers in the bladder-cancer group more closely approximates those present in the other groups of patients. It is clear that there is no association

TABLE 3.—*Percentage of Women Aged Forty-Five Years and Over with History of Cigarette Smoking by Class of Patient*

Class of Patient	No. of Patients	Cigarette Smokers	
		Unadjusted Percentage	Age-Adjusted Percentage
Bladder cancer	118	8.5	13.0
Benign bladder conditions	110	13.6	13.4
No disease	319	18.5	17.1
Breast cancer	776	12.4	12.3

of cigarette smoking with bladder cancer in women.

Duration of Cigarette Smoking.—In view of the finding of an association of cigarette smoking with bladder cancer in men, we thought it would be of further interest to determine if this relationship could be specified in terms of the degree and duration of the cigarette-smoking habit. These two measures would provide some index as to the influence of the amount of exposure. Such relationships have been described in the previously reported studies of the association of cigarette smoking and lung cancer.* Unfortunately, the data on amount of cigarettes were inadequate for analysis, and, therefore, the only measure that furnishes some indication of the influence of the extent of exposure is that of the length of time that a person has smoked.

The percentages of men who smoked cigarettes less than and more than 30 years in the various patient classes are presented in Table 4. We note that the age-adjusted percentage of bladder-cancer patients who smoked less than 30 years is 11.2, as compared to a range of 7.2%-7.8% in the other patient classes. These differences are not statistically significant (Table 5). However, the age-adjusted percentage of those who smoked more than 30 years was 49.4%, as compared to 35.7% of the no-disease and prostate-cancer groups, which differences are statistically significant (Table 5). We also note that the excessive percentage of cigarette smokers in the lung-cancer group is likewise limited to the group who smoked more than 30 years. It would thus appear that the excess frequency of cigarette smokers in both the bladder- and lung-cancer groups exists with regard to those persons who have smoked more than 30 years.

A similar analysis was carried out for the women, and the data are presented in Table 6. The percentages of women who smoked more than 30 years are so low that it was not particularly appropriate to carry out any age adjustment. It appears that the percentage of women who smoked cigarettes for more than 30 years was no different in the bladder-cancer group than in the

* References 3 and 4.

TABLE 4.—*Percentage of Men Who Smoked Cigarettes Less than and More than Thirty Years, by Class of Patient*

Class of Patient	No. of Patients	Per Cent Cigarette Users	
		Less than 30 Yr.	More than 30 Yr.
Unadjusted Percentage			
Bladder cancer	307	10.4	47.9
No disease	328	9.5	36.6
Prostate cancer	281	4.3	31.0
Lung cancer	301	8.6	74.8
Age-Adjusted Percentage			
Bladder cancer	307	11.2	49.4
No disease	328	7.8	35.7
Prostate cancer	281	7.2	35.7
Lung cancer	301	7.3	75.2

TABLE 5.—*Comparison of Percentage of Men with Bladder Cancer and Those With No Disease Who Used Cigarettes Less than and More than Thirty Years*

Duration of Cigarette Use, Yr.	Weighted Mean Difference, %	S.E.*	P†
Less than 30	+0.033	0.025	0.20
More than 30	+0.136	0.039	<0.001

* S. E. indicates standard error of weighted mean difference.
† P indicates probability that the difference could have arisen by chance alone.

TABLE 6.—*Percentage of Women Who Smoked Cigarettes More than Thirty Years, By Class of Patient*

Class of Patient	Total No. of Patients	Per Cent Who Smoked Cigarettes for More than 30 Yr.
Bladder cancer	116	1.7
Benign bladder conditions	109	1.8
No disease	317	2.5
Breast cancer	763	0.9

other types of patients. It is possible that the low percentage of women who smoked for 30 years or more is the reason for the absence of an association of cigarette smoking with bladder cancer in women.

Comparability of Patient Groups.—In interpreting the finding of an association of cigarette smoking with bladder cancer in men, it is important that the classes of men being compared are alike with respect to other factors that may influence the frequency of cigarette smoking. We have taken such factors as age and sex into account in our comparisons. It is difficult to determine what other factors would be sufficiently important to warrant their being taken into account in this type of analysis. However, the present material does permit us to compare the patient classes with regard to both the population size of the area of residence and the socioeconomic status of the patients residing in Buffalo.

The comparison of the patients with regard to population size of the area of residence provides some indication of whether or not there exist differences in the rural-urban distribution of the patient classes. This is of some interest in view of the possible existence of differences in tobacco use habits in rural and urban communities. In Table 7 there are presented the percentage distributions of the different classes of patients by size of population group. We note that the distributions for all of the patient classes are essentially similar, with the exception of lung-cancer patients. In this instance, there is a distinct tendency for more of these patients to come from the more urbanized areas. However, even if there is an increased cigarette-smoking frequency in these areas, the differences in distribution by population size do not appear great enough to account for the relatively higher frequency of cigarette smoking among lung-cancer patients.

The other factor that could be studied with the present material was that of socioeconomic status. In this instance it was necessary to limit our consideration to those patients who resided in the city of Buffalo, since this city is one of the metropolitan areas on which the Bureau of Census publishes information concerning the characteristics of the census tracts. For each census tract there are available certain socioeconomic indexes, such as median monthly rental, occupational data, and home ownership, by means of which the population may be classified into socioeconomic

TABLE 7.—*Per Cent Distribution of Classes of Men by Size of Population Group of Residence*

Size of Population Group of Residence	Class of Patient									
	Bladder Cancer		Benign Bladder Conditions		Prostate Cancer		Lung Cancer		No Disease	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
100,000 and over	96	31.4	14	35.0	87	33.7	115	39.8	113	35.9
50,000–99,999	16	5.2	4	10.0	14	5.4	24	8.3	15	4.8
25,000–49,999	26	8.5	6	15.0	26	10.1	25	8.7	25	7.9
10,000–24,999	33	10.8	3	7.5	17	6.6	44	15.2	21	6.7
2,500– 9,999	59	19.3	5	12.5	48	18.6	34	11.8	64	20.3
Under 2,500	76	24.8	8	20.0	66	25.6	47	16.3	77	24.4
Total	306	100.0	40	100.0	258	100.0	289	100.1	315	100.0

groups. Admittedly this method of classification furnishes only a rough approximation of the socioeconomic status of these patients, but it does permit the determination of whether marked differences in the socioeconomic distribution are present. This is of interest, since there may be differences in tobacco-use habits in the various social strata. In view of the small number of cases in each patient class, it was only possible to determine the per cent of patients who were in the upper and lower socioeconomic halves of the city population; these are presented in Table 8. We note

TABLE 8.—*Distribution of Different Classes of Men from Buffalo by Socioeconomic Status*

Socioeconomic Status	Class of Patient							
	Bladder Cancer		Prostate Cancer		No Disease		Lung Cancer	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Upper half	47	58	39	50	55	52	42	43
Lower half	34	42	40	50	51	48	56	57
Total	81	100	79	100	106	100	98	100

that more of the bladder-cancer patients came from the upper socioeconomic half and that more of the lung-cancer patients came from the lower socioeconomic half. However, these differences are not statistically significant.

Comment

These data appear to indicate that there exists an association of cigarette smoking with bladder cancer in men, which association is of a lower degree than that found with regard to lung cancer. In addition, this association is limited to those persons who have smoked cigarettes for a period of 30 years or longer. Prior to discussing the implications of these results, it is important to emphasize that both the experimental study in mice and the analyses presented in this report require confirmation by similar investigations elsewhere.

In view of the reported observation concerning the experimental production of bladder cancers with intraorally applied tobacco tars, any inference from the presently reported statistical associations concerning a cause-and-effect relationship between cigarette smoking and bladder cancer in humans is considerably strengthened. In fact, the results of the present study have certain implications with regard to some of the criticism of the epidemiological studies of the association of cigarette smoking and lung cancer. For example, Berkson, who has recently reviewed these statistical studies in the case of lung cancer, placed a great deal of emphasis on the need for verification of statistical studies by animal experiments.[5] In the case of bladder cancer, we now have evidence based on both an animal experiment and a statistical study in humans, and, therefore, according to the type of reasoning employed by Berkson, this should indicate a cause-and-effect relationship. Acceptance of such a relationship may be taken as the demonstration of the existence of a carcinogenic agent in cigarettes. This in turn makes more reasonable the assumption that the observed association between lung cancer and cigarette smoking is likewise due to the presence of a carcinogenic agent. Obviously, if this is true, the statistical association of lung cancer with cigarette smoking demonstrated by hospital and other type of studies both retrospective and prospective must represent a true association and not a spurious one due to the operation of assumed selective factors.

Our own interpretation of these data is

that they are highly suggestive of a cause-and-effect relationship between cigarette smoking and bladder cancer. However, it is clear from the data presented that even if we accept cigarette smoking as a casual agent, it is not a specific agent in the sense that it is one whose presence is necessary for the production of the disease. This is indicated particularly in the case of women with bladder cancer where no association with cigarette smoking was found. In addition, other etiological factors are known to be involved.[6] In any further studies attempting to determine other etiological factors in bladder cancer, cigarette smoking will have to be taken into consideration.

Summary

Other investigators have reported the production of urinary bladder cancers in mice by the intraoral application of tobacco tar. In an attempt to determine if a similar relationship exists in humans, the clinical records of patients admitted to the Roswell Park Memorial Institute were reviewed. Analysis of these records indicated that a significantly larger proportion of men with urinary-bladder cancer smoked cigarettes than did other classes of patients chosen for comparison. This association was limited to those who gave a history of having smoked for 30 years or more. This association was of a lower degree than that found in the case of lung cancer. In a similar analysis of women with bladder cancer no association was found. The implications of these findings are briefly discussed.

Addendum

Analysis of the occupational status of the men at time of admission to the Institute indicated no significant differences between the various classes of patients.

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The Incidence of Blood Group A in Pernicious Anemia

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Introduction

In 1953 Aird and Bentall reported a significantly higher incidence of blood Group A in patients with cancer of the stomach than in the general population.[1] Since cancer of the stomach is three to four times as common in pernicious anemia as in the population at large,* the incidence of blood Group A in pernicious anemia is of some interest. Such a study forms the basis for this report.

Method

Patient records which had been filed under the heading "pernicious anemia" at the Stanford University Hospitals (1937-1955), the University of California Hospital (1934-1955), and the San Francisco Hospital (1942-1954) were examined.† Specific information sought included the presence of macrocytic anemia, achlorhydria after histamine injection, combined system disease, megaloblastic bone marrow, hematologic response to adequate therapy, atrophic gastritis, glossitis, the impression of the attending physicians, and the determination of blood group.

Of 524 records which had been filed under the heading "pernicious anemia" at the three institutions, 115 contained a blood group determination and also satisfied the indicated diagnostic criteria sufficiently to be regarded as representing cases of pernicious anemia. The blood group distribution of 20,070 donors appearing at the Irwin Memorial Blood Bank,‡ in San Francisco, from January through June, 1955, provided control values.§

Results

Table 1 presents a comparison of the percentage distribution of ABO blood groups in 115 cases of pernicious anemia and 20,070 normal blood donors. It can be seen that the percentage of persons who are Group A is 35% higher in the cases of pernicious anemia than in the normal blood donors. This preponderance of blood Group A in pernicious anemia appears to

TABLE 1.—*Percentage Distribution of ABO Blood Groups in 115 Cases of Pernicious Anemia and 20,070 Normal Blood Donors*

Blood Groups	Pernicious Anemia, % Positive	Normal Blood Donors, % Positive
O	37.4	47.2
A	51.3	38.1
B	10.4	10.6
AB	0.9	4.1

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* References 2 and 3.

† Miss Helen B. Martin, of the University of California Hospital, and Mrs. Dorothea Johnson, of the San Francisco Hospital, made hospital records available for this study.

‡ Miss Dorothy Day, of the Irwin Memorial Blood Bank, San Francisco, supplied the 1955 control data for this report.

§ It will be noted that the case records of pernicious anemia assembled cover two decades in time, whereas the control determinations were all obtained in 1955. In order to make certain that the percentage distribution of blood groups in the general population had not changed over the last decade or two in San Francisco, owing to altered techniques of blood typing, differences in typing sera, or shifts in population make-up, 900 blood group determinations from 1939-1940 and 1942-1943 were gathered from the records of the Stanford University Hospitals. The percentage distribution of this older set of data did not differ by more than 1% for any group incidence from the 1955 figures given.

occur mostly at the expense of blood Group O. For this difference in incidence, $P>0.1$ and <0.025, a significant difference. Table 2 compares the incidences of

Higley's data show a higher incidence of blood Group A in cases of fibroid uterus and in instances of jaundice from all causes than in pernicious anemia.[5] In the latter

TABLE 2.—*Percentage Distribution of ABO Blood Groups in Cancer of the Stomach and Pernicious Anemia*

Disease	Blood Group, %								Cases, No.
	O		A		B		AB		
	Disease	Control	Disease	Control	Disease	Control	Disease	Control	
Pernicious anemia	37.4	47.2	51.3	38.1	10.4	10.6	0.9	4.1	115
Cancer of the stomach (Holländer, 1953)	36.22	41.65	53.12	45.06	7.53	9.03	3.13	4.26	704
Cancer of the stomach (Aird, 1953)	42.95	46.78	46.19	41.38	7.76	8.79	3.10	3.05	2745

the various blood groups in pernicious anemia with those found in two large studies of blood group frequencies in cases of cancer of the stomach. In the latter two studies the incidence of blood Group A was 18% || and 11% (Aird and Bentall[1]) higher than in the respective control groups, both increases in per cent of blood Group A thus being considerably less than the 35% increase in incidence of blood Group A found in the present study of pernicious anemia.

No specific attempt was made in this study to relate the incidence of the D antigen to pernicious anemia. However, it may be noted in passing that the incidence of the D antigen in 56 patients with pernicious anemia was within 2% of the incidence in the controls.

Comment

The present finding of an increase of 35% in the incidence of blood Group A in pernicious anemia over that in normal donors has not been previously reported. Clarke and co-workers do say that "in 457 cases of pernicious anaemia Buchanan and Higley (1921) reported a higher incidence of Group A than in other conditions which they investigated."[4] Actually, Buchanan and

|| Holländer: Personal communication to Aird and Bentall.[1]

regard, the authors themselves say, "The percentages . . . demonstrate that the causal factor in pernicious has no relation to blood-grouping." We have calculated that for their figures $P<0.20$ and >0.10, a level indicating no significant difference between the incidences of the blood groups in pernicious anemia and in normals. It is not entirely clear why Buchanan and Higley's findings and those presented here are not similar. Several reasons may be suggested: Their cases of pernicious anemia were seen at the Mayo Clinic, while as their control figures they used Moss's data gathered elsewhere.[6] In addition, blood typing procedures and sera may have altered somewhat in the last 35 years.

The increased incidence of blood Group A in pernicious anemia is not an observation that will affect clinical or laboratory diagnosis of the disorder very deeply. The finding described in this report is insufficiently characteristic to be helpful to the clinician, but it should be of considerable interest to those concerned more wtih the pathogenesis of the disease. It is of course part of the lore of pernicious anemia that it is a condition almost confined to persons with blue eyes, blond, early-graying hair, and family origins in northwestern Europe. One might propose that the increased incidence of blood Group A is another such characterisic

and means no more than blue eyes or being born in Denmark. Yet several points may be stressed before the blood group observation is so lightly dismissed. The relation of blue eyes and blond hair to pernicious anemia is far more strict than the relation of blood Group A to this disorder. Blood Group A has a considerable incidence in the Far East, e.g., India and China,[7] where there is little or no occurrence of blue eyes, blond hair, or pernicious anemia.¶ Equally worthy of emphasis is the observation that nowhere in northwestern Europe is the incidence of blood Group A as high as in our pernicious anemia series, with the sole exception of the Lapps, a small dark brachycephalic people.[7] Hence there is some support for believing that the significance of the increased incidence of blood Group A in pernicious anemia is not identical with that of some other physical characteristics of the disease.

In view of the data of Aird and Bentall concerning the increased incidence of blood Group A in cancer of the stomach,[1] and also in view of vaguely analogous pathologic changes in the stomach in both cancer and pernicious anemia,[10] reference must be made to the relation of cancer of the stomach and pernicious anemia in the light of the finding of the present report. These two disorders have been related for two reasons: the increased incidence of the former in the latter disease # and the loss of certain gastric secretory abilities in both conditions. It has been tacitly assumed, if indeed any assumption has been examined, that the relationship is a direct one. But with the observations that the incidence of blood Group A is elevated in both disorders there exists an alternative interpretation: that both cancer of the stomach and pernicious anemia are each related directly (though not exclusively) to the occurrence of blood Group A and only indirectly to each other. There are several bits of evidence which support this point of view. In the Far East, where there is for practical purposes no pernicious anemia, cancer of the stomach varies in its incidence in a suggestive way with the frequency of blood Group A. Quisenberry's data for cancer of the stomach as percentage of all cancers in the Japanese, Chinese, and Filipinos of the Hawaiian Islands are, respectively, 34.5, 12.4, and 5.7.[11] Mourant's percentage frequencies for blood Group A in Japanese, Chinese, and Filipinos are, respectively, 28, 20, and 14.[7] From these necessarily slim data there is yet a hint that the incidence of cancer of the stomach, in a single, circumscribed area, varies directly with the incidence of blood Group A. It seems improbable that this proposed association is the only important influence on the incidence of gastric cancer. There are undoubtedly environmental factors, as Woolf's recent work suggests.[12] Before one takes the above formula for the whole truth, one might recall the 42% frequency of blood Group A in the United States with 12% of all cancer deaths being due to stomach lesions,[13] as compared with the Japanese blood Group A frequency of 28% with 34.5% of all cancer deaths being due to stomach lesions.

There is another observation that is consistent with the contention that gastric cancer and pernicious anemia are each related to the occurrence of blood Group A rather than directly to each other. Aird's figures show 11% higher incidence of blood Group A in cases of cancer of the stomach than in controls;[1] the present report's data demonstrate an increase of 35% in the incidence of blood Group A in pernicious anemia over that in normal blood donors. Thus the excess of blood Group A in pernicious anemia is three times that in cancer of the stomach, and, as is well known, the incidence of gastric cancer in pernicious anemia is roughly three times that in the rest of the population.* This observation may then suggest again that cancer of the stomach and pernicious anemia are each related to the

¶ References 8 and 9.

References 2 and 3.

* References 2 and 3.

occurrence of blood Group A rather than being more directly related. In this connection, Mosbech prophesied such a relationship without naming it. He says: "the excess mortality from gastric carcinoma in patients witht pernicious anemia may be genotypic, depending on a common inherited predisposition to the two diseases."†

Grossly, then, what is the contrast in genetic factors between gastric cancer and pernicious anemia? The relation of blood Group A to cancer of the stomach may be world-wide, whereas the relation of blood Group A to pernicious anemia obtains only for persons of that blood group from a certain geographic area and possessing certain eye, hair, and cephalic characteristics. So one might propose that pernicious anemia is an expression of (at least) the gene for blood Group A plus another gene related to hair, eyes, etc., with perhaps varying combinations of penetrance of these genes all able to produce pernicious anemia. In contrast, the association of blood Group A and cancer of the stomach does not seem to require the accompaniment of any other factor for expression, or at any rate no other factor is yet suspected aside from environmental ones.[12]

It is difficult to put into clear language any other possible association between blood Group A and pernicious anemia beyond a sort of ineluctably direct relation of the blood group to depression of gastric secretion. The mind runs to such thoughts as these: A-like substances are widely spread in nature; could antibodies made against a slight variant of exogenous A substance cause failure of intrinsic factor manufacture, a factor recently suspected of being chemically similar to A-substance?[15] Or, is intrinsic factor manufactured and released inversely to its tissue or blood level—analogous to certain hormones? In this fancy, native A-substance (if secreted?) might have an inhibitory effect on intrinsic factor manufacture or release.

An analogous relating of cancer of the stomach to the possession of blood Group A can also seem tendentious. Certain data, those of Aird and Bentall[1] and the direct variation of gastric cancer and blood Group A in the Far East,‡ have already been advanced in support of a fairly direct relationship. Obviously there must be other possibly environmental influences, too, and so it may prove stimulating to consider possible mechanisms of pathologic physiology whereby these two conditions may be related. If A-substance and intrinsic factor are indeed chemically similar, and are both secreted by the stomach, then gastric atrophy may cause failure of secretion of both. The effects of "retained" A-substance that is normally secreted may be important. Could it become an in situ carcinogen? Another thought would be this: When A-substance (or intrinsic factor, too, if different?) is no longer mixing with the dietary stream, are dietary carcinogens no longer bound or neutralized, This latter conjecture might explain the local occurrence of the carcinoma, but one wonders about the cases of achylia in which gastric cancer does not develop and the gastric cancers that occur in persons of blood Groups O and B.

From all this discussion, one can at least ask certain questions in sufficiently clear form that rather specific observations might give fairly clear answers. Some of these questions are as follows: Is the incidence of gastric cancer in pernicious anemia much higher in those of Group A than in those of Groups O or B? What is the secretor-nonsecretor ratio in pernicious anemia and gastric cancer, if enough gastric fluid can be recovered for study? Can anti-A-bearing material be shown to have an in vivo inhibitory effect on intrinsic factor production? Are the usual proportions of Groups A_1 and A_2 represented in pernicious anemia and gastric cancer? What can be learned from a world-wide graphing of the relationship of blood Group A to cancer of the stomach? What of can-

† Reference 14, p. 92.

‡ References 7 and 11.

cer of the stomach in diabetes, with the latter's increased frequency of blood Group A [16] and achlorhydria?[17] What is the concentration of A-substance, in the gastric mucosa in pernicious anemia? Can A-substance, given by mouth or parenterally, depress manufacture of intrinsic factor? What is the incidence of cancer of the stomach in those animals possessing A-substance and in those which do not? What is the chemical effect of gastric juice on known carcinogens? These are some of the questions whose answers might supplement Woolf's emphasis on environmental influences in gastric cancer: "the quantitative effect of this (genetic) component is small. This leads to the conclusion that exogenous factors are of greater etiological importance."[12] The data presented in this report cast some doubt on the propriety of Woolf's view that the influence of the genetic component is small. It must also be remembered that ABO frequencies vary sharply over small geographic areas, while Rh frequencies vary little over the same areas.[7] This suggests that the ABO genes are relatively intensively selected by the environment, ie., these blood groups may be associated closely with, or even partially govern the occurrence of certain mortal diseases, examples of which may be gastric cancer and diabetes.

Summary

The incidence of blood Group A was found to be 35% higher in 115 patients with pernicious anemia than in the control group of 20,070 normal blood donors.

The significance of the observed increase in incidence of blood Group A in pernicious anemia is thought not to be identical with that of the characteristic hair and eye color and ethnic origin of persons with the disorder.

The increased incidence of blood Group A in pernicious anemia as demonstrated in this report, and the previously reported increased incidence of the same blood group in gastric cancer, is interpreted as suggesting that both gastric cancer and pernicious anemia may be related to the occurrence of blood Group A rather than being directly related to each other.

Various conjectures are offered on the mechanism of connection between blood Group A and pernicious anemia and on some possible links of physiologic derangement between blood Group A and gastric cancer.

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Syncope

A Study of Its Relation to Cardiac Disease

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Syncope, or common fainting, is a sudden, usually brief episode of unconsciousness due to a transient dysfunction of certain vital centers. These dramatic episodes never fail to provoke both lay and professional interest. Admittedly the caues of syncope are as varied as the circumstances which surround each appearance of this state. The excellent monograph of Engel [1] carefully scrutinizes the many etiologic factors involved in the production of this symptom.

That syncope occurs as a manifestation, symptom, or coexistent sign of cardiac disease is usually the thought of the layman rather than the physician. Many of the textbooks of medicine and cardiology regard syncopal attacks to be of little importance or of doubtful significance to the cardiologist unless associated with complete heart block, ventricular tachycardia, or the syndrome of carotid sinus hypersensitivity. Recently, however, more attention is being given to the fact that the cardiac arrhythmias may precipitate or be associated with syncope.* As a result of the relatively minor role assigned to the cardiac causes of syncope, an interest was stimulated and this study undertaken. The aim was to determine the relative frequency, in everyday cardiologic practice, of syncope caused by or associated with cardiac disease or functional disorder of cardiac rhythm.

The material upon which this article is based consists of 123 patients referred to the author for cardiac evaluation because of single or repeated episodes of fainting. The only patients included in this study were those who presented syncope as the only or major complaint. The selective nature of this investigation made it necessary to extend this work over a period of eight years.

Forty-two of the one hundred twenty-three patients studied were found to have either organic heart disease or a paroxysmal disorder of cardiac rhythm. Thirty-nine patients were diagnosed as having a cardiac arrhythmia; two had painless myocardial infarctions, and one patient had aortic valvular stenosis with first-degree atrioventricular block. The 39 patients displaying disorders of the normal cardiac mechanism were included only after demonstration of the electrocardiographic abnormality, either on initial visit or at the time of a subsequent syncopal attack. The two patients with myocardial infarction denied any experience of pain before or after the syncopal attack which accompanied the infarction. It is of particular interest that one of these patients had a second, painless, but fatal myocardial infarction. The one patient with aortic valvular stenosis (P-R interval of 0.24 second) and experienced fainting only with exertion.

The incidence of cardiac disease or of disorder of the heart beat found in the 123 routine cardiac consultations requested because of syncope is 34.15%. The statistical analysis of the various cardiac disorders found in the positive group of patients is indicated in Table 1. Table 2 reveals the

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* References 2 and 3.

TABLE 1.—*Type of Disease or Disordered Rhythm*

Type	Occurrence	Digitalis Toxicity	Proved Organic Heart Disease
Complete A. V. block	5		5
Atrial fibrillation	17		16
Atrial flutter	1		1
Atrial tachycardia	8*		1
Atrial tachycardia with block	2	2	2
Sinoatrial block	1	1	1
A. V. block, 2 degrees	1		1
Nodal tachycardia	1		1
Ventricular tachycardia	3	1	3
Aortic stenosis	1†		1
Myocardial infarction	2		2

* One patient had a Wolff-Parkinson-White syndrome.
† A. V. Block, 1 degree, also present.

TABLE 2.—*Incidence in Various Age Groups*

Type	18–25 Yr.	25–35 Yr.	35–45 Yr.	45–60 Yr.	60–80 Yr.
Complete A. V. block				3	2
Atrial fibrillation	1	2	1	4	9
Atrial flutter				1	
Atrial tachycardia	6*	1		1	
Atrial tachycardia with block				1	1
Sinoatrial block					1
A. V. block, 2 degrees					1
Nodal tachycardia		1			
Ventricular tachycardia	*			2	1
Aortic stenosis				1	
Myocardial infarction			1	1	

* Age of the patient with W.P.W. syndrome was 20 years.

age brackets into which patients with the disorders are classified. It is immediately recognizable that the 45-60 year and 60-80 year groups comprise the majority. The one case of sinoatrial block, two of atrial tachycardia with block, and one of ventricular tachycardia were definitely due to digitalis toxicity. The discontinuance of this drug, together with other therapeutic measures, resulted in disappearance of the arrhythmias and associated syncopal attacks. The one instance of ventricular tachycardia due to digitalis toxicity was the outcome of an attempt at suicide, by taking an undisclosed number of tablets of digitoxin (0.2 mg.) which had been prescribed for this patient. The arrhythmia persisted for 70 hours before reverting back to normal sinus rhythm.

Whereas 16 of the 17 patients with paroxysmal atrial fibrillation proved to have organic heart disease, only one with paroxysmal atrial tachycardia had unmistakable evidence of organic cardiac disease. This finding is in accord with the commonly known fact that paroxysmal atrial tachycardia may frequently disrupt the rhythm of a normal heart. The selective type of patients utilized in this study explains the high incidence of organic heart disease in the group.

Comment

This study reflects a rather high incidence of cardiac disease or dysfunction in a series of patients referred for cardiac appraisal because of the complaint of fainting. The narrow scope and selective nature of the investigation prohibits any correlation between these results and the over-all percentage of cardiac disease or disorder that might be found in the vastly greater number of patients seen because of syncope by the general practitioner of medicine. It does indicate, however, that cardiac abnormalities make up more than a negligible percentage of the many causes of fainting. This percentage will likewise increase and more closely approximate the figures of this study as the age group of the patients

increases. The important relationship between syncope and the onset of a cardiac arrhythmia in older patients is manifested readily by a review of the age group analysis. Syncope is particularly likely to occur in older patients with the onset of any of the rapid-rate arrhythmias. The cardiac rate in these instances is abruptly increased beyond the critical level where cardiac output adequately supplies cerebral blood flow demand. This fact alone should alert the physician to such a possibility and make an electrocardiographic study a necessary part of the postsyncopal survey of every older patient. Frequently both the syncopal attack and the arrhythmia have cleared upon the arrival of the physician, and several such trips are necessary before the rewarding graphic evidence is obtained.

The frequent appearance of ventricular tachycardia as a sign of digitalis toxicity in the diseased heart has previously been emphasized.[4] Likewise, the atrial arrythmias have come to play a prominent role in the detailed study of overdigitalized patients.† The associated appearance of syncope in some patients displaying these arrhythmias should direct one's attention to these possibilities in a search for the etiologic factor of fainting in patients known to be taking this drug. Similar attention is commanded by the association of syncope and frequent ventricular premature contractions.

Complete atrioventricular block with Stokes-Adams-Morgagni attacks, initiated by cardiac arrest or ventricular fibrillation, is the most universally known and ominous type of cardiac syncope. Other diseases and disorders of the heart, however, may produce equally disastrous results if the heralding symptom of fainting is not regarded sufficiently and investigated.

The finding of a high percentage of the paroxysmal atrial tachycardia with syncope in age group 18-25 years is significant. It should impress one with the facts that fainting in youth may be a disorder of physiologic function as well as, if not as often as, it is a psychologic deviation. Lastly, it is worthy of mention that, in the two cases of myocardial infarction included in this study, syncope served as a pain equivalent and gave the clinical picture of "silent myocardial infarction." That such occurs, even in a few instances, makes the thorough investigation of fainting mandatory before relegating this symptom to a benign status.

It is well understood that physiologic criteria to establish a cause-and-effect relationship between the existing cardiac abnormality and syncope are lacking in this report. Should such intensive investigation of each subject have been made available, the relationship might still remain controversial. Despite this deficiency, however, the coexistence of the two conditions must be admitted, and it is believed the following conclusions are justifiable.

Summary and Conclusions

A study was undertaken to determine the percentage of patients who, referred for cardiac survey because of syncope, displayed evidence of cardiac disease or dysfunction.

Forty-two of one hundred twenty-three patients so referred were found to have either cardiac disease or a disorder of the heart beat. This represents an incidence of 34.15%.

The high incidence of organic heart disease in this study group may be explained on the basis of the selective nature of the investigation.

It is concluded that cardiac diseases or disordered cardiac rhythms make up more than a negligible percentage of the causes of syncope, especially in older patients.

The initiation of a rapid rate arrhythmia is frequently associated with syncope in aging people.

Syncope may accompany, and attract attention to, the arrhythmias due to digitalis toxicity.

Syncope, unless surrounded by unmistakable evidence of its etiology, should warrant a search for cardiac abnormalities,

† References 5, 6, and 10.

which may be either causative or coexistent factors.

318 W. Godfrey Ave. (20).

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The Glomerular Lesions of Diabetes Mellitus

Cellular Hyaline and Acellular Hyaline Lesions of "Intercapillary Glomerulosclerosis" as Depicted by Histochemical Studies

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The reports of Kimmelstiel and Wilson [1] and Murakami,[2] in 1936, established the identity of special glomerular lesions in association with diabetes mellitus. Since then considerable interest has centered about the location, composition, and pathogenesis of glomerular changes in diabetes. In this communication we wish to record the results of the application of a series of histochemical procedures to the kidneys from six diabetic subjects. Sections from these kidneys, prepared by the usual techniques, demonstrated the glomerular lesions of diabetes as described in the literature.*

The findings presented herein serve to add emphasis to the presence of a multiplicity of ingredients within certain of the diabetic glomerular lesions. The observations reflect on the general problem of vascular hyalin by distinguishing further between "cellular hyaline lesions" and "acellular hyaline lesions" within the glomeruli. Also, additional support for the smooth-muscle origin of certain forms of vascular hyalin is presented.

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* References 1-20.

Review of Literature

Different points of view have evolved since the discussions of 1936.† In order to attempt to establish the relationship of the present findings to various available descriptions and interpretations, a general review of the literature appears appropriate at this time.

Composition and Location of Glomerular Lesions of Diabetes

Kimmelstiel and Wilson (1936) designated the spherical hyaline lesions which they observed in the kidneys from eight diabetics as "intercapillary glomerulosclerosis" because they interpreted the source of the lesion as sclerosis and hyalinization of the "intercapillary connective tissue" of the glomerulus. Allen [3] (1941) demonstrated the presence of an endothelial-lined lumen within the lesion by means of serial sections and interpreted the evolution of the nodule as due to a progressive thickening of the capillary wall. Allen [3] also reemphasized certain features of the lesion and added to an understanding of its make-up. These aspects may be summarized as follows: (1) The lesions are cellular, but the cellularity varies, consisting mainly of two or three concentric layers of flattened cells at the periphery and an occasional nucleus within the core. (2) A concentric fibrillar structure can be demonstrated by silver stains. (3) The nodular lesion is essentially collagenous but during its development it may contain ingredients possessing staining properties of noncollagenous type. (4) The nodule resists tryptic digestion in contradistinction to

† References 1 and 2.

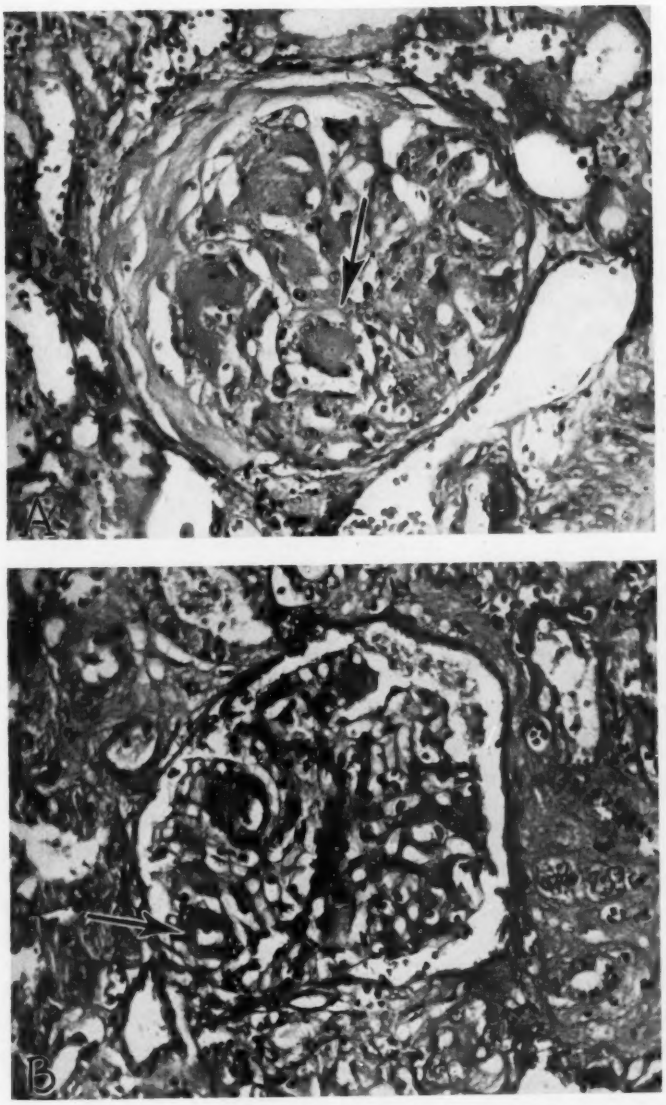

Fig. 1.—Hematoxylin and eosin stain; reduced approximately ¼ from mag. × 350. *A*, glomerulus displaying several cellular hyaline nodules. Two of the nodules reveal eccentric lumina. The nodule singled out by the arrow depicts dilated capillaries about its periphery. *B*, the structure singled out by the arrow represents a thickened capillary which is considered to represent a developing nodule. This structure is surrounded by open capillaries. Above it there is a more advanced stage of the cellular nodule, showing the peripheral cells, the hyaline core, and an eccentric endothelial-lined lumen. Another cellular hyaline nodule is seen at the upper extremity of the glomerulus. The right half of this glomerulus displays the diffuse type of thickening.

other glomerular structures. (5) Crescentric sudanophilic deposits may be observed in Bowman's space, but in general the nodule either has no fat or only scattered minute droplets of fat. (6) There are capillary loops at the periphery of the nodule, and some of these may be prominently dilated. Points (1), (3), (5), and (6) were discussed by Kimmelstiel and Wilson.[1]

Bell‡ (1946, 1953) distinguished between nodular and diffuse types of "intercapillary lesions." The nodular lesion was considered almost specific for diabetes. Bell[5] agreed with Allen[3] on the capillary origin of the nodules, probably from the "inner basement membrane." The diffuse lesion may progress

‡ References 4 and 5.

to complete obliteration of the glomerulus without the formation of nodules; however, Bell [4] stated that the "nodular lesions are formed from the diffuse by continuous splitting of the basement membranes."

It is agreed that diffuse and nodular changes occur in chronic glomerulonephritis, but Bell,[5] as well as Allen,[3] considered these alterations different from the diabetic lesions in number, location, and relationship to other local glomerular structures and changes. Kimmelstiel and Porter § (1948) stated "that intercapillary glomerulosclerosis may occur in a significant number of cases in chronic glomerulonephritis," and referred to Laipply, Eitzen, and Dutra [8] (1944) and Henderson, Sprague, and Wagener [9] (1947) to support this view. Moreover, after considering clinical as well as morphologic features, Kimmelstiel and Porter [6] were inclined to assume "that the same process of intercapillary glomerulosclerosis that occurs in diabetes also occurs in chronic glomerulonephritis."

McManus [10] (1950) supported the intercapillary origin of the nodular lesion. When subjected to the periodic acid-Schiff (PAS) procedure the nodule yielded positive results. The identification of PAS-positive material within the nodule represented the sixth general constituent noted within nodules up to that time (regular collagen, noncollagenous substance, cells, reticulin, sudanophilic material, and PAS-positive material). McManus and Saunders [11] (1950) also demonstrated digestion of the nodule by pectinase, a point of difference from the "glomerular basement membrane."

An additional outstanding feature of the glomerulus in diabetes has been emphasized by Koss [12] (1952). This author distinguished between the "nodular" lesion and the "hyaline-fibrinoid" lesion. Koss recognized that the lesion designated as "hyaline-fibrinoid" had been discussed by others under different designations. Thus, he considered that Kimmelstiel and Wilson [13] (1936) had discussed it within the designation of "alterative glomerulitis." Fahr [14] (1942) recognized it as a distinct change. Spühler and Zollinger [15] (1943) designated this change as "glomerular fibrinoid caps." Wernly [16] (1944) distinguished between the nodular lesions and the "hyaline glomerular caps." G. F. M. Hall [17] (1952) referred to the same lesion as the "exudative lesion" of glomeruli in diabetes. This is apparently the same change as the "crescentric sudanophilic deposits in Bowman's space," mentioned by Allen.[3] Bell [5] referred to this lesion as "acidophilic hyaline masses."

G. F. M. Hall [17] considered the "exudative lesion" to be composed entirely of "fibrinoid" and lipid. Part of the lipid component was shown to be doubly refractile. Distinction between the nodular and exudative lesion included in addition the central location of the former and the peripheral location and tendency toward a crescentric shape of the latter.

Barrie, Aszkanazy, and Smith [18] (1952) discussed the same lesion under two designations, the "fibrin cap" and the "capsular drop." The "fibrin cap" was described as covering the convex outer borders of the capillary loops. It stained like fibrin with phosphotungstic acid hematoxylin (dark blue). Frequently this structure contained sudanophilic vacuoles, but it was not invaded by cells. The "capsular drop" was described as a similar lesion developing in relation to the basement membrane of the capsule and having the same staining characteristics. This material, however, was invaded by cells and became fibrous in time. This lesion apparently was considered by Kimmelstiel and Wilson [1] under the heading of "capsular changes."

Koss [12] differentiated the nodular and hyaline-fibrinoid lesions by their staining characteristics. The nodular lesion usually yielded the staining reactions of con-

§ References 6 and 7.

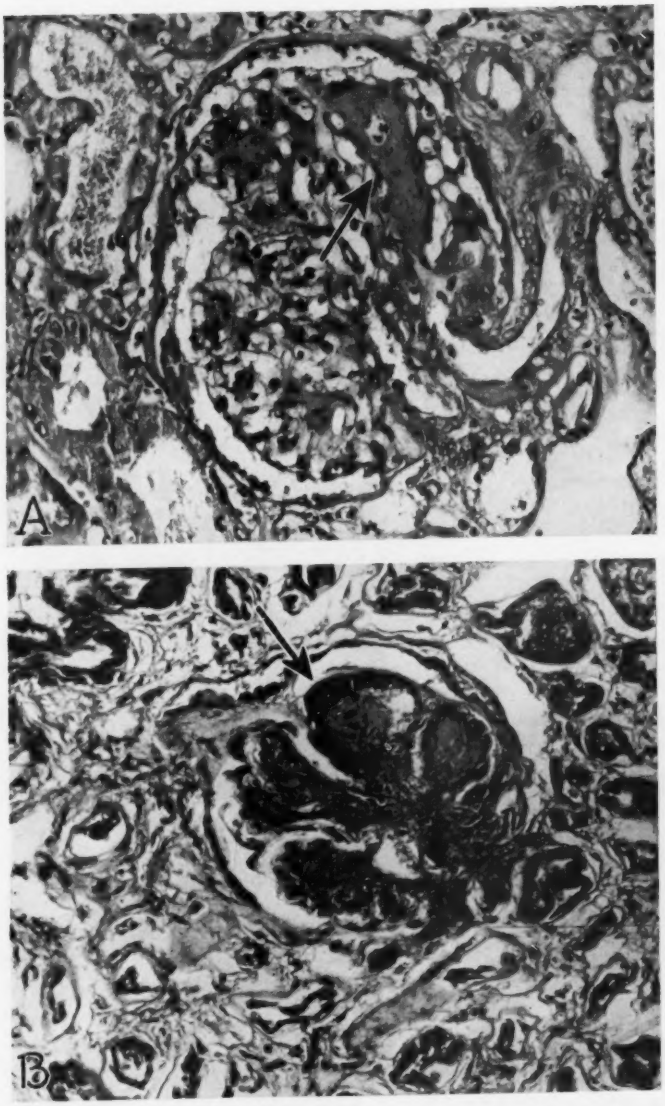

Fig. 2.—*A*, hematoxylin and eosin stain; reduced approximately ¼ from mag. × 350. The elongated structure pointed out by the arrow is considered as a cellular hyaline nodule. There is a well-depicted endothelial-lined central lumen. The peripheral cells form two layers, and a few scattered central cells are seen in the hyaline core. The nodule to the left of this structure is prominently cellular. The attached arteriole is demonstrated to be hyaline. *B*, Mallory stain; reduced approximately ¼ from mag. × 350. This glomerulus reveals two cellular hyaline nodules which are surrounded by the acellular hyaline masses. With this stain the former stain blue and the latter, intensely red. The structure pointed out by the arrow reveals four crescentic or oval masses of the acellular hyaline material. This configuration suggests to us that the material is within the capillaries surrounding the cellular nodule. The similar appearance of the hyalin in the arteriole (above and to the left of the glomerulus) and the glomerular hyalin is shown.

nective tissue, while the hyaline-fibrinoid lesion gave the characteristics of so-called "fibrinoid," such as an intensely eosinophilic appearance, an intense red color with the trichrome stain, a yellow color with Van Gieson stain, and a fibrin color with Weigert's stain and phosphotungstic acid hematoxylin. Koss [12] noted the cellular nature of the nodular lesion and the acellularity of the fibrinoid lesion. At times the hyaline-fibrinoid material surrounded the nodular lesion as a crescentric mantel. The hyaline-fibrinoid material was considered to be located in the walls of the capillaries rather than in the lumina. It was Koss' view that the hyaline-fibrinoid lesions had been frequently confused with the nodular diabetic lesion.

Wilens, Elster, and Baker [19] (1951)

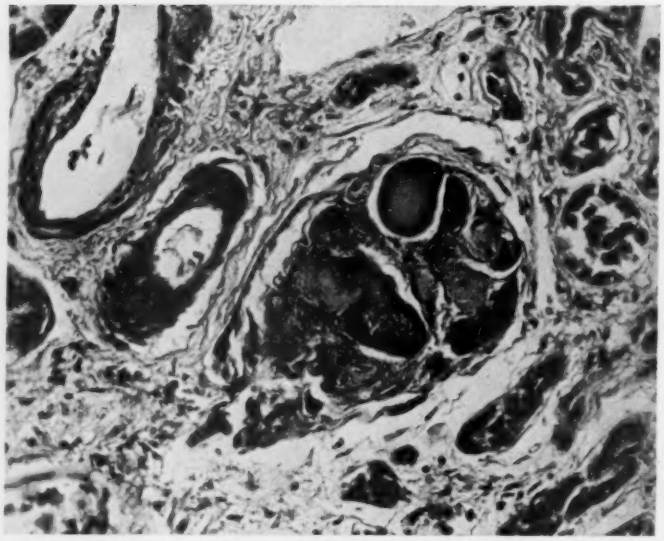

Fig. 3.—Mallory stain; reduced approximately ¼ from mag. × 350. This figure demonstrates prominent deposits of the acellular hyaline masses within a glomerulus which is otherwise destroyed by cellular nodules and diffuse fibrosis. The hyaline arteriole shown has a segment with the same appearance as the acellular hyaline in the glomerulus. There are free globs in Bowman's space as well as others surrounding and closely affiliated with the cellular nodules. The vacuolated appearance of the hyalin is also depicted.

took exception to the casual treatment in the literature of glomerular lipid deposits. These authors attempted to determine the quantity of sudanophilic material (lipid) within glomeruli in different renal diseases. A significantly greater amount of lipid was noted in "intercapillary glomerulosclerosis" of diabetes when compared to other renal diseases, such as glomerulonephritis and arteriolar nephrosclerosis. Moreover, the quantity of glomerular fat was directly proportional to the severity of the diabetic lesions in most instances. It should be noted that Kimmelstiel and Wilson[1] were also impressed by the fat content as indicated by the statement "fat stains (Sudan III) usually give a homogenous pinkish color, while double refraction is only exceptionally present in smaller circumscribed areas."

Anderson[20] (1954) encountered nodular glomerulosclerosis much more commonly than the exudative type. In addition he emphasized "globular masses of hyaline substance in Bowman's space" and "localized capillary dilatations, similar to those demonstrated by Hückel."[21] As a rule only one aneurysm was observed per glomerulus. In the majority of cases the walls of the aneurysms were markedly thickened by a hyaline substance, usually, but not always, covered by endothelium.

Two types of aneurysmal dilatations within the glomeruli have been described. Anderson[20] described a structure similar to that described by Hückel.[21] This aneurysm is characterized by a widening of a main vessel near the hilus of the glomerulus which at the same time is lined with a hyaline deposit similar to the hyalin of the arteriole. The hyalin of the arteriole may be continuous with that of the "aneurysm." This type of lesion is not confined to diabetic subjects. || Aneurysms similar to this type have been described in retinal vessels by Friedenwald.[22] The other type of "aneurysm" has been described by Allen[23] (1955). This is represented by a widening of a capillary or capillaries within the lobule, near one of the cellular nodules. Allen interprets this "aneurysm" as secondary to obstruction of blood flow resulting from the nodule. At the same time he proposes the obstruction as a source for increased

|| Muirhead, E. E.: Unpublished data.

Fig. 4.—Lipid as demonstrated by oil red O.

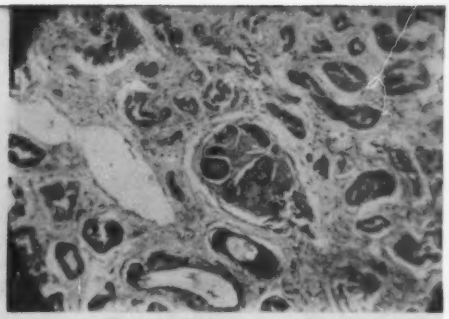

Fig. .8—Free aldehyde group as demonstrated bv the periodic acid-Schiff reaction on paraffin section tissue (same lesion as in Figure 3).

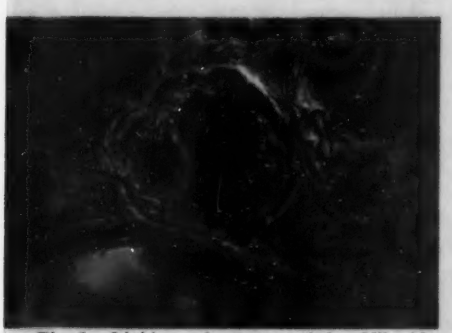

Fig. 5.—Lipid as demonstrated by Nile blue sulfate.

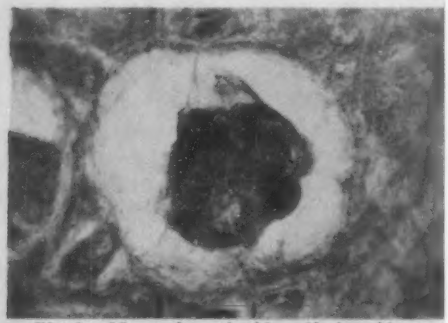

Fig. 9.—Mucopolysaccharide sulfuric acid ester as demonstrated by Congo red stain.

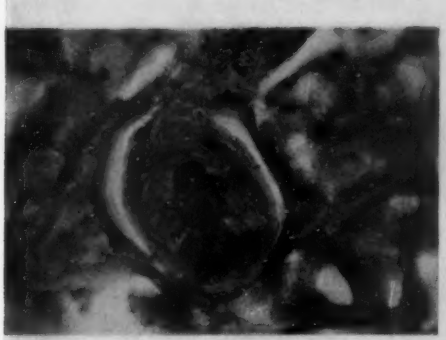

Fig. 6.—Lipid as demonstrated by Sudan black B.

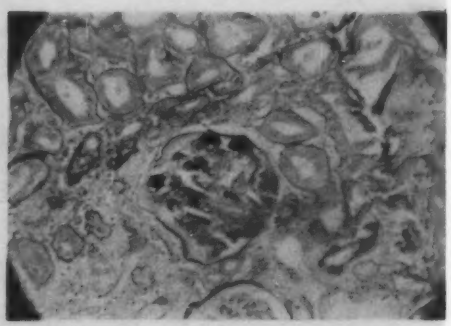

Fig. 10.—Protein-bound sulfhydryl group as demonstrated by the reaction of Barnett and Seligman.

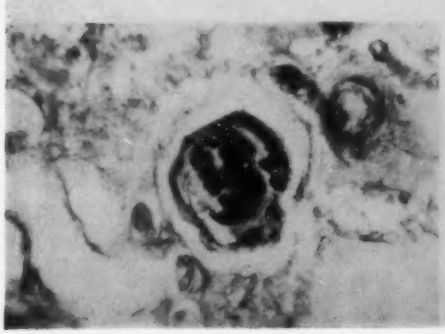

Fig. 7.—Potassium as demonstrated by Gomori's modification of MacCallum's method.

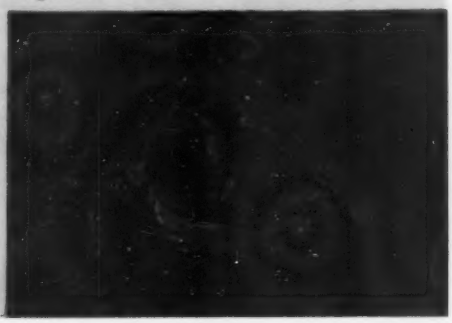

Fig. 11.—Free carbonyl group as demonstrated by the reaction of Ashbel and Seligman.

permeability to plasma protein, a causal factor in the coexistant proteinuria.

Location and Pathogenesis

Little is known about the specific cause and detailed evolution of either hyaline glomerular lesion.

Kimmelstiel and Wilson [1] considered the nodular lesion as degenerative without specifying the factors in the "degeneration." Allen [3] and Bell ¶ considered the source of the nodular substance as the capillary wall without identifying specific factors influencing thickening of this structure. These workers, however, indicated a relationship between hyaline arteriolosclerosis of the afferent arteriole and the nodular lesions. Bell [4] was willing to state that "the arteriolar disease in some way brings about the 'intercapillary' lesions, but a severe arteriolarsclerosis (Grade 3) did not produce glomerular lesions of any kind in one-third of the cases." Horn and Smetana,[24] on the other hand, discussed the encounter of intercapillary sclerosis in association with nondiabetic type of arteriolarsclerosis. Goodof [25] described mild lesions in 10% of the population, while severe lesions were confined to diabetics.

G. F. M. Hall,[17] howover, could accept neither hypertension nor arteriolosclerosis as etiologic factors for the diabetic lesions. To this observer it appeared more likely that "diabetic glomerulosclerosis in some way produces arteriolosclerosis." Poor diabetic control, on the other hand, appeared as a potent etiologic factor. Laipply, Eitzen, and Dutra [8] earlier agreed with this view. They stated "that it (renal arterial and arteriolar sclerosis) is of basic importance seems unlikely, but its being a contributing factor cannot be excluded."

Although Allen [3] and Bell # do not accept the presence of connective tissue in the intercapillary space of the glomerulus normally, they, nevertheless, look upon the nodule as collagenous and cellular. Since the combination of collagen and spindle cells represents the composition of connective tissue, these workers by implication leave the necessity for some local source for connective tissue in the development of the nodule.

The "hyaline-fibrinoid" lesion (synonyms: "fibrinoid caps," "fibrin cap," "exudative lesion," "acidophilic hyaline masses") has been the subject of different pathogenetic considerations. Koss [12] emphasized four additional sites of deposition of a similar type of "hyaline-fibrinoid" substance, namely, in the parietal layer of Bowman's capsule, in the basement membrane of the proximal convoluted tubules, within arterioles displaying marked arteriolosclerosis, and in certain of the casts within the tubules. Koss preferred to consider the "hyaline-fibrinoid" as derived from the protein of an exudate accumulating between the separated endothelial and epithelial basement membranes of the glomerulus. The pathogenesis was thus considered related to the permeation of various structures by protein from the plasma. The presence and deposition of fat was considered a secondary phenomenon. This view gained support from the observations of Churg and Grishman,[26] which considered the hyalin of intercapillary glomerulosclerosis as an albuminoid substance deposited from the blood. Duguid and Anderson [27] also supported the hematogenous origin of the hyalin of arteriolosclerosis.

Wilens, Elster, and Baker [19] suggested that the deposition of fat in the glomeruli may be of primary importance in the development of the lesions of intercapillary glomerulosclerosis. The glomerular lipid was considered most likely associated with the hyperlipemia of diabetes. Also the combination of lipemia and elevated intraglomerular pressure was thought to afford an opportunity for the lipid to penetrate into the intercapillary space. Penetration of lipids into the walls of arteries was considered also to

¶ References 4 and 5.

References 4 and 5.

evolve by a similar mechanistic process, events subsequent to the lipid deposition differing in the avascular arterial wall as compared to the richly vascular glomerulus. Since a significant incidence of hyaline arteriolosclerosis without "intercapillary glomerulosclerosis" occurs in diabetes, as earlier noted by Bell,[4] Wilens and co-workers speculated on a possible explanation. In those cases in which the hypertension and arteriolosclerosis antedated the hyperlipemia the glomeruli may have been protected (pressurewise) from the deposition of lipid, thus offering an explanation for the absence of "intercapillary glomerulosclerosis."

Anderson[20] considered the "exudative lesion" to differ from the nodular lesion in degree rather than in kind. The capsular lesion was shown to have a phase during which it consisted of free globs in Bowman's space. Anderson considered that the material was extruded from the capillary aneurysm of the glomerulus and became attached to Bowman's capsule and subsequently was covered over by epithelium, thus assuming an appearance of having originated within the capsule.

The cause of the capillary aneurysm was considered unknown by Anderson.[20] The sequence of the hyaline deposition within the aneurysm was also unknown, although a suspicion that the arteriolar and glomerular changes resulted from the deposition of a protein coagulum from the blood was expressed.

Observations on experimental animals impinge on this problem. Lukens and Dohan[28] described hyaline deposits within the glomerular capillaries in a dog made diabetic for five years with extracts of the anterior lobe of beef pituitary glands. The hyalin formed rings or crescents next to the capillary lumen as well as being deposited irregularly. Cellular proliferation also was present. Mann and Goddard[29] described glomerular lesions in rats made diabetic with alloxan monohydrate. Reticulin proliferation and hyaline-like balls entrapped in the intercapillary and axial spaces were described. Sussman and Freed[30] described globular lesions in the glomeruli of rabbits made hyperglobulinemic. These lesions resembled the nodular lesions of intercapillary glomerulosclerosis. Rich, Berthrong, Bennett, Cochran, Griffith, and McGoon[31] reported aneurysmal dilatation of glomerular capillaries and nodular lesions following the use of cortisone in experimental glomerulonephritis. Bloodworth and Hamwi[32] produced lesions in the glomeruli of normal rabbits by the administration of cortisone. The lesions were thrombotic and composed of mucopolysaccharides and lipid within dilated capillaries. They resembled the human "exudative lesions" of diabetes. Wilens and Stumpf[33] pointed out the association of the cortisone-induced glomerular lesions in the rabbit and the lipemia also induced by the hormone. Hartroft[34] encountered fat emboli in glomerular capillaries in choline-deficient rats. The lesions evoked by the emboli resembled both the diffuse and nodular types of the Kimmelstiel-Wilson lesion in diabetic man. The liver was considered the likely source of the emboli. Fat in the lumina of glomerular capillaries was encountered in 75% of diabetic subjects with Kimmelstiel-Wilson disease. Hartroft[34] entertained the possibility that plugging of glomerular capillaries by fat either entrapped as emboli or precipitated in situ initiated the events leading to the Kimmelstiel-Wilson lesions in diabetic man.

Clinical Features

Kimmelstiel and Wilson[1] recognized a relationship between the glomerular lesions they described and a clinical syndrome characterized by diabetes, severe and widespread edema of the nephrotic type, and gross albuminuria. Hypertension was frequently present. There soon followed other attempts to correlate the glomerular lesions with the clinical manifestations of diabetic subjects.

Anson[35] encountered "intercapillary glomerulosclerosis" in the kidneys of 6 of 900 cases. Only two of the six cases displayed the nephrotic syndrome. Derow, Altschule, and Schlesinger[36] emphasized the

presence of the nephrotic syndrome in their one case of diabetes with nodular glomerular lesions. Laipply, Eitzen, and Dutra,[8] however, encountered the nephrotic syndrome in only 6.3% of 332 cases.

Newburger and Peters[37] analyzed the clinical features of 18 cases coming to autopsy and 5 other cases not subjected to postmortem examination. The clinical features emphasized were the diabetic state, albuminuria, hypertension, and retinal vascular changes. The nephrotic syndrome was common, but its development was considered related to the duration of the albuminuria and the protein intake. These authors stated: "The pathogenesis of this condition appears to depend on severe and extensive arterial and arteriolar degeneration, associated with and perhaps resulting in diabetes mellitus, hypertension and renal damage." Since this paper concerned itself with the relationship between the glomerular changes and the clinical state, this statement appears as an appreciation of the position of arteriosclerosis in the genesis of the morphologic as well as the clinical manifestation of the glomerular renal disease of diabetes.

Siegal and Allen[38] failed to encounter the nodular lesions in the absence of diabetes or hypertension. The nodular lesion was observed twice in the apparent absence of clinical diabetes. These two cases were presented as evidence against diabetes as the sole etiologic factor in the development of nodular glomerulosclerosis. The lesion was encountered in one-third of the diabetics studied and in 12 of 60 diabetics without hypertension. A definite relationship was observed between the degree of involvement of the kidneys with nodular glomerulosclerosis and the clinical picture of diabetes, severe and widespread edema, and albuminuria.

Kimmelstiel and Porter[7] analyzed the main clinical correlation available in the literature up to that time (1948). An over-all incidence of 17.1% was given for the lesion. It occurred overwhelmingly in the older age group (peak incidence at age 65). Although the nephrotic syndrome occurred in only 10% of the cases verified by autopsy, it was significant that no cases of diabetes with nephrosis had been recorded in which intercapillary glomerulosclerosis was not demonstrated. Retinopathy occurred in 86% of the cases, hypertension in about 60%, significant albuminuria in 66%, edema of the nephrotic type in less than 10%, impaired renal function in 50% to 75%, and uremia in less than 20%. Thus the statement: "It is, therefore, correct to state that there are no definite clinical features to establish the diagnosis of intercapillary glomerulosclerosis." This was the position taken by Bell[5] and Porter and Walker.[39] This attitude is also supported by the extensive clinical study presented by Rifkin, Leiter, and Berkman.[40] Rogers and Robbins[41] not only found no clear-cut clinical syndrome but encountered clinical features commonly attributed to glomerulosclerosis in diabetic patients who failed to display the glomerular lesions at autopsy.

Rogers, Robbins, and Jeghers[42] observed no correlation between the severity of the diabetic state and the frequency of intercapillary glomerulosclerosis. The general view that the incidence increases with increasing diabetic years was supported; only 14% of patients with diabetes of less than 4 years' duration showed intercapillary glomerulosclerosis, while a 64% incidence was noted in diabetics of 10 to 14 years' duration.

Methods

The formalin-fixed blocks of kidney tissue were obtained from the autopsies of six patients with long-standing clinical diabetes mellitus and with the morphologic lesions of nodular intercapillary glomerulosclerosis. The clinical record of each case related clear-cut support for the diagnosis of diabetes mellitus; each patient had been managed with insulin.

For comparison, similar blocks of renal tissue were obtained from the autopsies of six patients whose kidneys showed the morphologic picture of severe chronic pyelonephritis as described by Weiss and Parker[43] and Saphir and Taylor.[44] Many glomeruli in the latter examples revealed fibrous replacement. None of these patients was suffering from diabetes mellitus.

Frozen sections of the formalin-fixed blocks of tissue were then studied by a variety of histo-

chemical techniques as described in the standard texts * or as given by specific references.

The lipid components of the lesion were studied by the following procedures: oil red O, Nile blue sulfate, Schultz, Sudan black B. Free aldehyde groups were demonstrated by the periodic acid-Schiff reaction. Sulfuric acid esters of mucopolysaccharides were stained by the Congo red stain. Free carbonyl groups were demonstrated by the method of Ashbel and Seligman.[46] Potassium was demonstrated by McCallum's method as modified by Gomori.[48] Protein-bound sulfhydryl groups were demonstrated by the technique of Barrnett and Seligman.[49]

Permanent sections of formalin-fixed tissue embedded in paraffin were stained with hematoxylin and eosin, Mallory's stain, Masson's trichrome stain, and the periodic acid-Schiff reagent.

Results

The glomeruli from the six diabetic cases comprising the basis of the present report contained the two distinct lesions discussed repeatedly above in the section on the Review of the Literature. We prefer to consider one lesion as the "cellular hyaline lesion," a term which corresponds to the main lesion described by Kimmelstiel and Wilson and Allen, and the nodular lesion of Bell and Koss. The other lesion we prefer to consider as the "acellular hyaline lesion," a term which corresponds with Koss' "hyaline-fibrinoid lesion," Fahr's and Spühler and Zollinger's "glomerular fibrinoid caps," Wernly's "hyaline glomerular caps," Hall's "exudative lesion," Barrie, Aszkanazy, and Smith's "fibrin cap," and Bell's "acidophilic hyaline masses."

Acellular Hyaline Lesions ("Hyaline Fibrinoid" Lesions).—This lesion is deeply eosinophilic and intensely red with either Mallory's or Masson's stains. It assumes different shapes. Frequently it is globular or crescentic, being either within the periphery of a glomerular lobule or seemingly capping over its capillary structure. At times it is free in Bowman's space, as discussed by Anderson, or it may be attached to the Bowman's capsule. This lesion, however, can appear spherical or nodular and can be entirely within a glomerular lobule. On occasions the material appears elongated and spread out or smeared within the lobule. Not infrequently this type of deposit surrounds the nodular and cellular lesion. The latter configuration gives the appearance of deposits of the acellular hyaline masses ("hyaline-fibrinoid") within the capillaries surrounding the cellular hyaline nodule. The material in other instances also seems to us to be within capillaries. It may appear finely granular, lumpy, or smooth and fused and frequently contains fine vacuoles.

The acellular hyaline lesion displayed a variety of ingredients as demonstrated by the histochemical procedures used. These included triglycerides, fatty acids, and phosphatides, as shown by positive staining with oil red O, Nile blue sulfate, and Sudan black B. The predominant color with Nile Blue sulfate was blue, suggesting that the major bulk of lipids present were of the acidic type. Cholesterol and cholesterol esters were demonstrated by a positive Schultz reaction.† The Schiff reaction was positive in both the frozen and the paraffin sections, indicating the presence of free aldehyde groups likely associated with polysaccharides, mucopolysaccharides, mucoproteins, glycoproteins, glycolipids, or unsaturated lipids. The Congo red stain was positive, indicating the presence of sulfuric acid esters of polysaccharide origin, thereby offering additional evidence for the presence of polysaccharide within the lesion. The reaction with Congo red has been reported as negative in the literature,[12] however, this may have resulted from failure to use frozen section, as in the present study. Free carbonyl groups were present, as indicated by a positive reaction utilizing the Ashbel-Seligman technique. Potassium was prominently present, as indicated by the positive reaction, using Gomori's modification of the MacCallum method. Protein-bound sulfhydryl was indicated by a positive reaction with the method of Barnett and Seligman.

* References

† The Schultz reaction is not entirely specific for cholesterol, but cholesterol and its esters seem to account for a major part of the color developed by a positive action.

The work of Koss [12] and others has indicated that these lesions yield additional tinctorial properties, such as a deep blue color with phosphotungstic acid hematoxylin, a positive Weigert stain for fibrin, a yellow color with the Van Gieson stain, a blue or faintly purple reaction with toluidine blue, and a smooth and pale response with the silver stains.

The Composition of the Acellular Hyaline Lesion and That of Hyaline Arteriolarsclerosis: With the hematoxylin and eosin stain both the acellular glomerular lesion and the arteriole displaying arteriolosclerosis have a hyaline appearance. These two structures are not only hyaline in appearance, but the type of hyalin of one closely resembles that of the other with this stain.

When a series of other stains are used, such as the Mallory stain, Masson's trichrome stain, the Van Gieson stain, the phosphotungstic acid hematoxylin stain, and others, the staining properties of the acellular hyaline lesion are similar not only to the hyaline arteriole but also to the necrotic arteriole of malignant hypertension. Previously, the staining and histochemical similarities between the necrotic and hyalinized arteriole were presented.‡

The present study demonstrates that various histochemical procedures yield the same results when applied to the acellular hyaline lesions of the glomeruli, the necrotic arteriole (arteriolonecrosis), and the hyaline arteriole (arteriolosclerosis). It appears, then, that similar and multiple ingredients are present within the necrotic arteriole, the hyalinized sclerotic arteriole, and the "acellular hyaline" lesion of the glomeruli from diabetic subjects.

Relation of Acellular Lesion to Casts in Tubules: Certain casts within the renal tubules were observed by Koss [12] to reveal the same staining properties as the "hyaline-fibrinoid" (acellular hyaline) lesion of the glomerulus. This observation has been confirmed in the present study. However, there were as many casts yielding a negative reaction as those yielding the same reaction as the acellular hyaline lesions. It is, therefore, of distinct interest that the same relationship existed with respect to the various histochemical procedures used. The positive findings were particularly noted in larger casts situated within dilated tubules where stasis is expected to occur. Casts within adjacent tubules varied in their reaction, some being positive, others negative.

The presence of similar material related to the basement membrane of the convoluted tubules as described by Koss was not noted in these studies.

Cellular Hyaline Lesions (Nodular Lesions).—The cells related to this nodular lesion are arranged mainly about its periphery, although scattered cells are frequently entrapped within the nodule. These features are well demonstrated by many photomicrographs available in the literature. The number of cells within the nodules varies between 1 and 12. Within the six kidneys of the present study, of 89 nodules 83 had a peripheral mantle of cells and 46 had cells within the core. The number of cells within the core varied between 2 and 14, but the average number was 8 for this particular group of nodules. It is this obvious relation of these nodules to spindle-shaped cells that led to the designation "cellular hyaline lesion."

The nodule, which varies between 20 and 200μ in diameter, is usually located near the center of a glomerular lobule and is surrounded by capillaries. The main bulk of the nodules is either fibrillar or smooth.

In the present study, just as in all studies in the literature, the collagenous characteristics of the nodule have been demonstrated. With the exception of an occasional nodule containing scattered lipid particles, the lipid procedures (oil red O, Nile blue sulfate, Sudan black B, and Schultz) were negative. A distinctly positive PAS reaction, which appeared as definite as in the acellular hyaline lesions, was noted. The Congo red reaction was negative, and the free carbonyl, potassium, and protein-bound SH proce-

‡ References 62 and 67.

dures yielded minimal or negative reactions which were distinctly less evident than with the acellular hyaline structures.

In all of its reactions the cellular nodular lesion responded in a manner identical to that of totally fibrosed glomeruli observed in the kidneys with chronic pyelonephritis.

Thus, the cellular nodular lesions had the characteristics of connective tissue and the hyaline lesions had the characteristics of the hyalin of the arteriolosclerotic (afferent) arteriole.

Frequency of Lesions: The incidence of each type of lesion was appraised by counting within slides from each case stained by the Mallory and Masson trichrome methods the number of glomeruli containing cellular nodular and acellular hyaline lesions. Within all slides appraised the over-all frequencies of cellular nodular and acellular hyaline lesions among more than 1000 glomeruli counted were 20% and 7%, respectively. Thus, the over-all ratio favored the cellular nodular hyaline lesion by about 3:1. The individual ratios, however, varied markedly (6:0, 14:1, 5:1, 2:1, 1:1).

Comment

This study adds support to the veiw emphasizing two distinct lesions within the glomeruli of diabetic subjects. One lesion tends to be nodular and is both cellular and collagenous. The other lesion is globular, crescentic, or elongated, contains no cells, and has the characteristics of the vascular hyalin found in arteriolosclerosis. Although the cellular hyaline lesion is commoner, the acellular hyaline structure is sufficiently encountered to assume a prominent position in any consideration of the kidney in diabetes.

The occurrence of a lumen within the cellular and nodular hyaline lesion, as described by Allen, has been confirmed. We agree with Allen that the variations of this configuration are in keeping with an origin from the capillary wall.

The collagenous nature of the cellular nodule suggests an origin from either "intercapillary connective tissue" or the capillary endothelium. An origin from capillary endothelium has not been demonstrated, although this possibility is not beyond consideration. For instance, in the evolution of the endarteritic type of pulmonary vascular sclerosis the endothelium appears to proliferate and lay down collagenous fibers.§ Under these conditions the endothelium seems to deposit concentric layers of connective tissue while maintaining the cellular lining of the vascular lumen. Should the endothelium in one area be able to deposit collagenous fibers it is reasonable to expect the same function elsewhere.

The cells entrapped within the nodule may be interpreted as lingering fibroblasts or endothelium, while the peripheral cells may represent original endothelium, proliferated endothelium, or compressed endothelium of nearby capillaries.

The structure of the glomerulus as recently proposed by B. Vincent Hall [53] may explain the common encounter of a mantle of capillaries about the cellular nodule. Hall considers the anatomical and functional units of the glomeruli to be the lobules. Within the lobules there are a few larger vessels (communicating vessels) which afford direct routes from afferent to efferent arterioles. These larger vessels give rise medially and internally to short capillaries which anastomose freely and form networks. The larger vessels are considered to facilitate a rapid flow of the main mass of plasma and cells directly through the lobules, while the smaller vessels, containing mainly plasma, may afford maximal opportunity for filtration. Within such an arrangement an expanding nodule would tend to be surrounded by capillaries.

While the cellular hyaline lesion is collagenous, the acellular hyaline lesion has been considered to be of "fibrinoid" composition. Thus it becomes necessary to consider the terms "fibrinoid" and "fibrinoid degeneration."

The term "fibrinoid degeneration"[54] has

§ References 50-52.

been used to depict a basic reaction to injury of connective tissue. The substance "fibrinoid" has been described as a "homogenous, eosinophilic, relatively acellular, substance with some of the tinctorial properties of fibrin."[55] Particularly it has stained like fibrin with Weigert's fibrin stain and phosphotungstic acid hematoxylin. It also stains yellow with Van Gieson's stain, intensely red with Mallory's stain and Masson's trichrome stain, homogenously red with periodic acid-Schiff reagent, and at times metachromatically with toluidine blue. According to Altshuler and Angevine[55] a common feature of "fibrinoid" formation is the precipitation of acid mucopolysaccharide of the ground substance of connective tissue.

The material "fibrinoid" has been described in many different lesions, including the lesions of rheumatic fever,[56] rheumatoid arthritis,,[57] periarteritis nodosa,[58] disseminated lupus erythematosus,[59] the generalized Shwartzman phenomenon,[60] and hypertension.[61]

In the various considerations of the "fibrinoid" change it is evident that this descriptive term has been used for alterations within connective tissue per se, as well as for changes within muscular blood vessels. We have obtained data, to be presented elsewhere,‖ which demonstrate that although connective tissue "fibrinoid" and vascular "fibrinoid" have certain similar staining and histochemical properties, there are major histochemical differences in their composition. For this and other reasons mentioned below, we prefer to distinguish between these two types of so-called "fibrinoid degeneration." In this discussion interest is directed primarily to the vascular type of "fibrinoid."

The necrotic arteriole of malignant hypertension occurring in man yields the staining characteristics of "fibrinoid." The staining and histochemical characteristics of this form of arteriolonecrosis are very similar to

‖ Montgomery, P. O'B., and Muirhead, E. E.: Unpublished data.

The Staining and Histochemical Characteristics of the Glomerulus in Diabetes, Fibrosed Glomeruli of Pyelonephritis and Arteriolar Lesions of Hypertension

Procedure	Diabetic Glomerulus Cellular Hyaline Lesion	Diabetic Glomerulus Acellular Hyaline Lesion	Pyelonephritis Fibrosed Glomerulus	Malignant Hypertension in Man; Nephrectomized Dog Arteriolonecrosis	Benign Hypertension in Man; Nephrectomized Dog Hyaline Arteriolosclerosis
Hematoxylin-eosin	Eosinophilic	Intensely eosinophilic	Eosinophilic	Intensely eosinophilic	Eosinophilic
Masson trichrome	Green	Intensely red	Green	Intensely red	Intensely red
Mallory's aniline blue	Blue	Intensely red	Blue	Intensely red	Intensely red
Oil red O	− or ±	+	−	+	+
Nile blue sulfate	−	+	−	+	+
Sudan black B	−	+	−	+	+
Schultz reaction	−	+	−	+	+
Periodic acid-Schiff	+	+	+	+	+
Congo red	±	+	±	+	+
Free carbonyl	±	+	±	+	+
Potassium	± (slight)	+ (Intense)	± (Slight)	+ (Intense)	+ (Intense)
Protein-bound SH	±	+	+	+	+
PTAH *	Yellow orange	Deep blue	Yellow orange	Deep blue	Deep blue
Silver *	+ (Fibrillar)	− (Smooth)	+	− (Smooth)	− (Smooth)
Toluidine blue *	Blue	Blue or faint purple	Blue	Blue	Blue (metachromasia)
Van Gieson *	Pink or red	Yellow	Red	Yellow	Yellow

* These procedures were not all included in the present study but have been recorded in the work of references 3, 12, 62, 65, and 67.

those of the hyalinized arteriole observed in either malignant or benign hypertension of man.[62] In time some connective tissue elements become admixed with the hyalin of arteriolosclerosis. These relationships between the necrotic smooth muscle of the media, so-called "fibrinoid," the hyalin of arteriolosclerosis, and connective tissue elements can be more definitely appreciated in the hypertensive cardiovascular state of the bilaterally nephrectomized dog.¶

In this experimental preparation, arteriolonecrosis, hyaline arteriolosclerosis, and varying mixtures of these two lesions can be observed depending on different means of managing the experimental preparation and the duration of survival.# Thus, by numerous observations arresting the injury and repair of the arteriole at different stages, a more precise relationship between these various arteriolar changes has been detected. The transitional changes between necrosis of the smooth muscle of the media and condensation of the necrotic muscle fibers have led to the conclusion that the hyalin is derived mainly from altered smooth muscle.[66] This view gained impetus when it was demonstrated that the necrotic arteriole of this preparation has the same staining, histochemical and microspectroscopic characteristics of the hyalinized arteriole.* Moreover, the staining characteristics of these two structures were those of so-called "fibrinoid."[66] We find ourselves, therefore, with the conclusion that the so-called "fibrinoid" of muscular vessels is derived mainly from alteration of the smooth muscle of the media occurring in situ.

It is of singular interest that staining as well as histochemical procedures reveal almost identical characteristics for the necrotic arteriole, the hyalinized arteriole, and the acellular hyaline lesion of the glomerulus. These similarities have been repeatedly demonstrated within the same microscopic section in the present study. Moreover, just as the necrotic arteriole may appear finely granular, finely vacuolated, or lumpy and granular, and the hyalinized arteriole may be either diffusely smooth or both smooth and crinckled in appearance, so the same span of appearances may be encountered in the acellular hyaline lesion of the glomeruli in diabetes.

The criteria now available lead us to the view that the arteriolar hyalin of diabetes and the acellular hyalin within the glomeruli of diabetics contain similar substances. The material in the arteriole appears to be composed mainly of the altered smooth muscle of the media. These considerations suggest that the acellular glomerular hyalin is derived from the arteriolar hyalin by the latter peeling off and embolizing the glomerular capillaries.

The suggestion of Anderson[20] that the free and attached capsular material is derived from the rupture of capillaries containing this material is not only reasonable but supported by additional findings. Thus, the encounter of a similar substance within certain but not all casts within the tubules is in keeping with a periodic escape of the substance in the glomerular capillaries with passage into Bowman's space and down the tubules to be admixed with casts. It is also reasonable to expect the passage of some of the material through the glomerular capillaries, followed by subsequent impaction or lodging within peritubular capillaries. The latter may explain Koss' finding of so-called "fibrinoid" outside of tubules and next to their basement membrane.[12]

Although both the cellular nodular lesion and the acellular hyaline lesion have been described within glomeruli in the nondiabetic hypertensive state, it is evident that diabetes contributes outstandingly to the frequency of both. No information concerning the manner in which the diabetic state accentuates these changes was obtained in this study. Moreover, any attempt to consider the pathogenesis of the cellular nodular lesion as related to the acellular hyaline deposits, even though attractive, would be speculative.

* References 67 and 68.
¶ References 63-68.
# References 63-67.

Conclusions

1. Two hyaline lesions are observed within the glomeruli of kidneys of diabetic subjects. One lesion tends to be nodular and is both cellular and collagenous. For this structure the term "cellular hyaline lesion" is preferred. The other lesion is crescentic, globular, oval, or elongated and is acellular. It has the same appearance as the hyalin of arteriolosclerosis. For this structure the term "acellular hyaline lesion" is preferred.

2. The "cellular hyaline lesion" is commoner than the "acellular hyaline" structure. In some kidneys, however, one lesion is as often encountered as the other.

3. The "acellular hyaline lesion" displays the staining characteristics of "fibrinoid." A series of histochemical procedures applied to this substance demonstrates the presence of multiple ingredients, such as triglycerides, fatty acids; phosphatides, cholesterol, and its esters; aldehyde groups likely associated with polysaccharides, mucopolysaccharides, mucoproteins, glycoproteins, glycolipids, or unsaturated lipids; sulfuric acid esters of polysaccharide origin; free carbonyl groups; free potassium, and protein-bound sulfhydryl groups.

The "cellular hyaline lesion" has the staining characteristics of collagen. The above histochemical procedures with this structure yield either negative or minimal results, except for the periodic acid-Schiff reagent procedure, which is positive.

4. The staining and histochemical characteristics of the "acellular hyaline lesion" are identical with those of the hyalin of hyaline arteriolosclerosis. The disposition of the "acellular hyaline material" is considered in keeping with an intracapillary position. It is suggested that the glomerular "acellular hyaline masses" are derived from the hyalin of the arteriole by embolization. Rupture of the material through the capillary wall can account for its presence in Bowman's space and certain tubules.

5. Reasons have been cited for the view that vascular "fibrinoid" is derived from altered smooth muscle of the media. The considerations of the present study suggest a similar origin from smooth muscle for the "acellular hyaline lesion" of the glomerulus of diabetic subjects.

6. The pathogenetic relationship between the "cellular hyaline" and "acellular hyaline" glomerular lesions of diabetes remains obscure.

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The Fate of Patients Surviving Acute Myocardial Infarction

A Study of Clinical and Necropsy Data in Two Hundred Fifty Cases

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Acute myocardial infarction has become increasingly well recognized clinically since Herrick's [1] stimulating paper was published in 1912. Although the interval of time since then should have afforded adequate opportunity for study of the final outcome in patients who survive the acute attack of myocardial infarction, and for study of the relationship between clinical observations and observations made at necropsy, there have not been many reports of such studies. It was the purpose of our study to obtain information as to what lies ahead for these patients. We have tried to determine what factors, if any, affected the course of surviving patients after acute myocardial infarction, particularly in regard to length of survival and manner of death. In addition, we have studied features of the pathologic cardiac anatomy and have correlated with them the clinical observations.

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Section of Medicine (Drs. Achor and Burchell) and Section of Pathologic Anatomy (Dr. Edwards), Mayo Clinic and Mayo Foundation; Fellow in Medicine, Mayo Foundation (Dr. Futch). The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Methods

Cases for study were selected from all necropsies performed at the Mayo Clinic from 1946 through 1950. To be included in the study, a case had to meet two primary criteria: (1) the heart had to present evidence of an earlier attack of acute myocardial infarction as manifested by the presence of a scar of not less than 2 cm. in length and 2 cm. in breadth and (2) the medical record had to be adequate as to history, physical examination, and information on terminal illness.

All the heart specimens were examined grossly in a manner similar to that described by Sheldon and Sayen,* that is, at least five serial sections transverse to the long axis of the heart were made through the ventricles. Each myocardial scar was measured in its greatest width and length, and an index of the size of the scar was obtained by multiplying these two values. To describe depth or thickness, each scar was classified as "transmural" or "subendocardial." On microscopic examination of a transmural scar the fibrosis was observed to extend throughout the section from the endocardial surface to the epicardium except where a thin layer of muscle survived beneath the adjacent endocardium. With subendocardial infarction the fibrosis was less extensive and was located nearer the endocardial surface than the epicardial.

In the classification of infarcts according to anatomic location the left ventricle was considered from the viewpoint of four major parts, namely, anterior, posterior, lateral, and septal. The anterior part was defined as that portion of the ventricular wall extending from the ventricular septum laterally to a point through the middle of the anterior papillary muscle. The posterior part was defined as that portion occupying the posterior wall and extending from the ventricular septum laterally to the lateral margin of the posterior papillary muscle. The lateral and septal parts were then designated as the portions remaining outside the two previously defined boundaries (Fig. 1). If there was scarring in the anterior and septal parts, the term "anteroseptal" was used. If anterior and

* References 2 and 3.

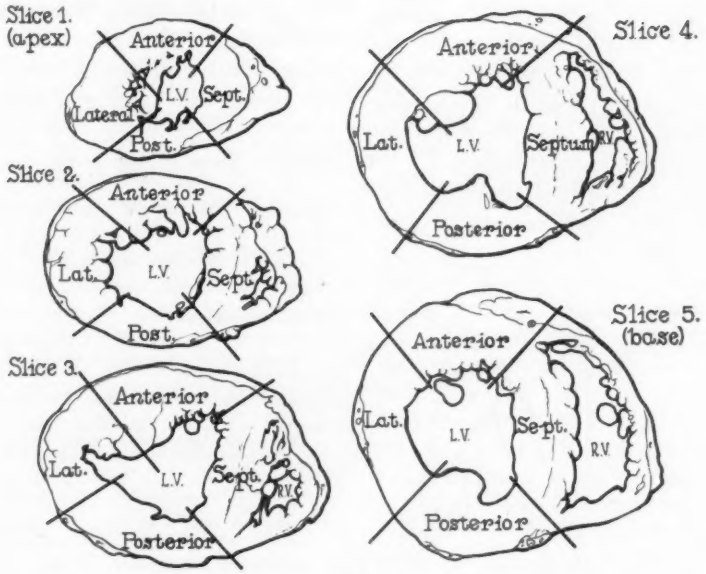

Fig. 1.—Diagram of ventricular "map" used to designate location of myocardial scars.

lateral parts were involved, the term "anterolateral" was applied. The same principle was employed in regard to the posterior half of the heart. It is realized, however, that such a classification cannot apply equally well in all cases because of the variation in anatomic location of the papillary muscles and also because the location of infarcts was occasionally very bizarre.

The coronary arteries of each heart were examined and found to be severely involved with atherosclerosis in nearly every case. This was to be expected, since the study was designed to select such cases. No attempt was made to correlate sites of coronary artery occlusion with sites of infarction.

Each heart had been weighed at necropsy, and the expected normal weight of the heart for that patient's sex and body weight was then determined from the tables prepared by Smith.[4] The difference between the actual weight of the heart and the expected normal weight was considered to represent the amount of myocardial hypertrophy. This difference was divided by the expected normal cardiac weight and multiplied by 100 to determine the degree of cardiac hypertrophy in per cent.

Specific examination and notation were made of any additional cardiac lesions, particularly with respect to recent myocardial infarction. Microscopic study was liberally employed to aid in establishing age and extent of infarction.

All the clinical records, the electrocardiograms when present, and the necropsy records were carefully evaluated in formulating the cause of death for each patient.

Results

Two hundred fifty cases, of which two hundred forty-eight patients were white and two were Negro, were finally selected from a total of 3355 necropsies performed; thus they represented 7.4% of the total necropsies.

One hundred ninety-two of the selected patients (77%) were men, and fifty-eight (23%) were women. However, in the entire necropsy series there were 2093 men (62%) and 1262 women (38%). Therefore, the 192 men of the selected group represented 9.2% of all necropsies performed on men, while the 58 women represented 4.6% of all necropsies on women; thus, the ratio of these percentages suggests that myocardial infarction is twice as common in men as in women. These figures are similar to those reported by Clawson and Bell[5] and by Wartman and Hellerstein.[6] Zinn and Cosby[7] found that the sex ratio was approximately 1:1 in their necropsy series. It would seem that when

necropsy material is used the commonly accepted high ratio of men to women who have coronary disease is not justified.

The average age at death in our series was 65 years, with 68% of all patients being past the age of 59 years (Fig. 2). The average age at death for men was 10 years lower than that for women.

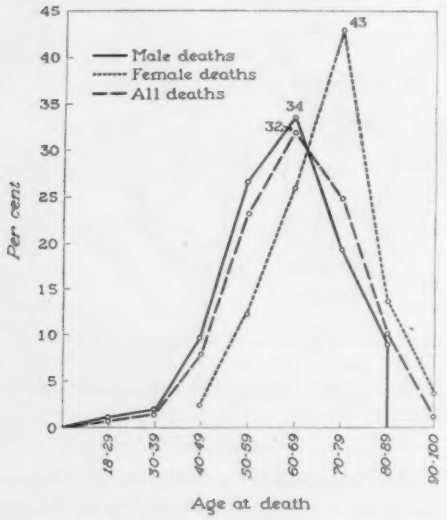

Fig. 2.—Age at death of 250 patients with myocardial scars found at necropsy.

Cause of Death.—Since both clinical and necropsy records were analyzed, it was possible to ascertain the cause of death in nearly all cases. For the most part, the causes of death seemed to fall in two categories, namely, those primarily of cardiac origin and those primarily of noncardiac origin. Both of these categories were subdivided to show more precisely the type of death (Table 1). There were 157 patients (63%) whose death was attributed to primarily cardiac causes and 93 persons (37%) whose death was attributed to primarily noncardiac causes. The average age at death of those who died of cardiac causes was 64 years, while the average age of the noncardiac group was 67 years. In the necropsy series reported by Zinn and Cosby,[7] 454 patients with myocardial infarction survived more than four months, and, of these, 287 (63%) were listed as dying primarily of cardiac causes. Employing Bean's data[8] and arranging them in a manner similar to that used in our study,

TABLE 1.—*Cause of Death in 250 Cases of Healed Myocardial Infarction*

Causes of Death	Cases	
	No.	%
Primarily cardiac causes		
Congestive heart failure without acute myocardial infarction	44	18
Death during episode of recurrent acute myocardial infarction	49	20
Acute cardiac death ("sudden death") without congestive failure or acute infarction	64	26
Total	157	63
Primarily noncardiac causes		
Postoperative complications*	34	14
Chronic illness, largely malignancy	15	6
Cerebral vascular deaths†	15	6
Infectious disease	10	4
Systemic vascular occlusion or rupture causing death‡	7	3
Miscellaneous	12	5
Total	93	37

Emboli from mural thrombus could not be excluded in two cases (*), seven cases (†), and one case (‡).

we find that of his 186 patients with old scars 66% died primarily cardiac deaths. Approximately 74% of all the patients with myocardial infarction reported by McCain, Kline, and Gilson[9] as surviving more than one month died of cardiac causes.

Primarily Cardiac Deaths.—The deaths attributed to primarily cardiac causes were, in general, of three fairly distinct types (Table 1). The first was that of congestive heart failure without acute myocardial infarction. The second type was that in which death occurred during an episode of recurrent acute myocardial infarction for which there was evidence on gross and histologic examination of the heart. The third type was less well defined but included deaths from an acute cardiac illness in which neither acute myocardial infarction nor congestive heart failure could be

implicated as the cause of death. These patients usually were thought to be quite well, but subsequently some were found dead in bed, and others died suddenly while up and about or died within a matter of minutes or hours after experiencing an episode of thoracic pain.

In the third group, consisting of acute deaths, the time interval between onset of the terminal illness and death was studied in order to determine the abruptness of the final episode, particularly since this group contained the cases of "sudden death." Of the 64 patients in the group, 50 had previously been quite well and then later had been found dead or else had died within an hour after onset of the acute illness. (Five of these fifty patients died immediately after a surgical procedure.) The other 14 patients died within 1 to 12 hours after onset of the acute distress. In these 64 cases recent coronary thrombosis was found in only 15 instances. Histologic examination of the myocardium in these cases, as well as in the other 49 cases of acute death, revealed no evidence of recent infarction. The observation that acute coronary thrombosis was present in only 23% of the cases of "acute death" emphasizes the "functional" mechanism of death in many patients with coronary artery disease. These deaths most likely are a result of major disturbances in cardiac rhythm arising from an ischemic myocardium. In several instances, fortuitous electrocardiograms showed ventricular fibrillation, ventricular standstill, and chaotic rhythms just prior to death. Contrasted with the group of those dying with congestive heart failure and the group of those dying with recurrent acute myocardial infarction, there is less known regarding the mechanism and treatment for patients in the group in which death occurs suddenly. It is suggested that this kind of death might be the subject of more intense study and a rewarding place to reduce the incidence of unexpected death among patients with coronary heart disease.

The second group, consisting of the 49 patients who died during the presence of acute myocardial infarction, presented a variety of manifestations leading to death. Of these, 22 died with congestive heart failure, 15 died relatively "sudden deaths," four died during a profound state of shock, and three died after rupture of the ventricular septum. Pneumonia and uremia were predominant factors in two cases each, and one patient died with pulmonary embolism. These findings conform to the observations of McQuay and associates [10] on types of death during acute myocardial infarction.

In the group of 44 cases in which death was attributed chiefly to congestive heart failure without acute myocardial infarction, hypertension was present in 27 cases and absent in 10, and there was uncertainty as to its presence in 7. In 10 cases there were valvular lesions, and in 1 case the heart showed marked deposition of amyloid. Four of the patients with valvular lesions also had hypertension. Thus, 77% of the 44 patients who died as a result of congestive failure could be considered to have other cardiac disease in addition to coronary artery sclerosis and healed myocardial infarction.

In the group of 49 cases in which death was attributed to recurrent acute myocardial infarction, 20 patients had definite hypertension, and 1 of these had an associated valvular lesion. Therefore, 40% of the patients in this group could be listed as having additional cardiac disease.

In the group of 64 cases in which acute cardiac death occurred, 26 patients were hypertensive and 3 more had valvular disease but without hypertension. Thus, 45% had additional heart disease.

These findings suggest that although coronary sclerosis and old myocardial scarring can by themselves result in congestive cardiac failure the combination of them with hypertension or valvular disease is much more likely to do so.

Noncardiac Deaths.—Patients who died from causes of primarily noncardiac origin

comprised 37% of all the 250 patients who had healed myocardial infarction (Table 1). The largest group in this category consisted of those who died of postoperative complications, and many of these were patients with malignant tumor or other severe illness that necessitated operation despite the risk involved. Another large group consisted of those whose fatal illness could be attributed to other manifestations of arteriosclerosis. Embolization originating from mural thrombosis in the left ventricle could not be entirely excluded in 10 of these patients. Though these cases might possibly represent deaths that could be attributed to cardiac causes, they were not so classified since absolute evidence of embolization was not established.

Thromboembolism.—The data regarding embolic episodes are presented separately because the primary causes of death already described were thought to be more basic, with the embolic phenomena occurring secondarily. Massive pulmonary embolism was present in 16 instances (6% of 250 cases). In six of these the embolism was present in patients dying of congestive heart failure, and in one it was found in association with acute myocardial infarction. Pulmonary embolism was the immediate cause of death in nine patients not classed as dying of cardiac causes. Small pulmonary emboli that did not contribute primarily to the patient's death were not considered in this group.

The problem of systemic arterial occlusion was difficult to evaluate, because it was not always possible to decide whether the occlusion resulted from embolization or thrombosis in situ. Thus, if ventricular mural thrombi were present together with systemic arterial occlusion it would not be possible entirely to exclude emboli originating from the heart as a cause of the occlusion. However, none of these cases were classed as having deaths of cardiac origin. In the tabulating of the cases of systemic arterial occlusion, only those occlusions that were considered to be a major cause of death were included. This eliminated many small splenic, renal, or cerebral infarcts that had no apparent influence on the patient's final illness. If we combine all instances in which systemic arterial occlusion was a major cause of death, whether thrombotic or embolic in origin, the term "thromboembolic episode" can be used. This would then include 15 cases of cerebral infarction, 3 cases of ischemic extremities, and 3 cases of occlusion of the superior mesenteric artery. By adding these 21 episodes to the 16 episodes of massive pulmonary embolism, a total of 37 thromboembolic episodes leading to the patient's death is obtained. This represents 15% of the total series of 250 cases.

Pathologic Anatomy of Heart and Its Relation to Cause of Death.—Location of Infarct: In the consideration of the various locations occupied by the myocardial scars, only the left ventricle and the ventricular septum were studied in detail, and for all practical considerations the entire ventricular septum was considered as being a completely integrated part of the left ventricle. Consequently, no data will be presented on infarction found in the right ventricle or the atria. Thirty-three of the hearts were found to have more than one significant myocardial scar, with a great many more showing patchy areas of fibrosis, but for purposes of listing as to location of the scar, only one, the most extensive infarct, was classified for each heart (Table 2).

Among the predominantly anterior infarcts, anteroseptal scars were by far the commonest and for the most part included a larger number of the most extensive infarcts. Consequently, a large part or all of the apex was involved with this type of scar. The solely anterior scars were often confined to the apical tip without extending proximally to involve the septum, and they were usually small.

A somewhat different situation pertained to the posteriorly situated scars in that the posteroseptal scars were the most numerous though not the most extensive. In addition,

TABLE 2.—*Location of Myocardial Scars, Extent of Infarction in Ventricular Wall, and Average Size of Scar*

Primary Site of Scar	Cases No.	%	Subendocardial Scars	Transmural Scars	Av. Size Index*
Anterior only	11	4	8	3	21
Anteroseptal	91	36	40	51	48
Anterolateral	14	6	11	3	37
Subtotal	116	46	59	57	44
Posterior	24	9	17	7	14
Posteroseptal	41	17	20	21	31
Posterolateral	29	12	15	14	46
Subtotal	94	38	52	42	31
Lateral	34	14	29	5	18
Septal	6	2	5	1	16
Total	250	100	145	105	34†

* Width of scar multiplied by length.
† Average for all scars.

the apex was infrequently infarcted in this group.

Scars confined entirely to the lateral ventricular wall were relatively small and were most often situated nearer the base of the left ventricle rather than toward the apex. Infarcts present only in the septum were uncommon, and they were small. However, the septum was involved in conjunction with other sites in 53% of all hearts. Thus some infarction of the ventricular septum was present in 55% of all hearts, making it the most commonly involved single portion of heart muscle. Likewise, the lateral wall was involved to some extent in 32% of all hearts, though this part was the least involved of the four major sites.

An effort was made to determine whether there was any correlation between location of the scar and the cause of death. There was no significant correlation in the series as a whole.

Extent of Involvement of Ventricular Wall: Subendocardial scarring (58%) was observed more frequently than transmural lesions (42%) among the 250 hearts comprising our series (Table 2). These two types of scarring were approximately equally common in patients dying of cardiac causes. In those dying of noncardiac causes, transmural infarcts were present in only 30% of cases. Of the total number of hearts with transmural scarring, 73% were associated with death of cardiac origin. The ratio of transmural to subendocardial scarring was approximately 1:1 in the three major groups of the cardiac causes of death. These data would suggest that transmural infarction would be more likely to result in subsequent death from cardiac causes than would subendocardial infarction of the myocardium.

Size of Scar: The size varied from 2 by 2 cm. to 15 by 10.5 cm., with a range in the index of size (width multiplied by length) from 4 to 157. The average for the 157 cases in which death was attributed to cardiac causes was 41, while that for the noncardiac category was 24. In the cardiac category the average of all size indices for patients dying primarily of congestive failure was 45 as compared with 37 for those dying of acute causes and 41 for those dying during recurrent acute infarction. The relation of size of scar to anatomic location is presented in Table 2. It appears that the larger infarcts were more frequently associated with cardiac death and that the largest average size was found among the patients who died with congestive cardiac failure.

Cardiac Hypertrophy: The average value for cardiac hypertrophy over expected normal for all 250 cases was 60%. For the category of deaths due to cardiac causes the average value for hypertrophy was 69%, and for the noncardiac category it was 46%. For the three groups within the cardiac category, the average value was 87% for patients with congestive failure, 63% for those who experienced recurrent acute infarction, and 61% for those who experienced acute cardiac death.

The fact that more pronounced hypertrophy was associated with deaths from cardiac causes than with deaths from noncardiac causes is probably accounted for by the higher incidence of arterial hypertension and congestive cardiac failure in the

group of patients who died of cardiac causes. The hearts of patients dying of congestive failure were much heavier than those found in any other single group, again partly because of the higher incidence of hypertension and valvular disease in these patients. When the patients with elevated blood pressure were eliminated, the value for cardiac hypertrophy was still significantly increased (49%), though considerably less than in those with hypertension (71%). These findings are in agreement with the conclusions of Davis and Blumgart [11] that severe occlusive coronary disease in the absence of other conditions producing cardiac hypertrophy can cause slight to moderate degrees of myocardial hypertrophy but that the heaviest hearts are encountered when congestive cardiac failure has been present. Connolly and Littmann [12] recorded similar observations in 1951.

Valvular Lesions: Twenty hearts presented definite valvular lesions, representing 8% of the 250 cases. Fourteen of these hearts were associated with cardiac deaths, and six, with noncardiac deaths. The aortic valve alone was involved in 12 instances, the mitral valve alone in 5, and both valves in 3. The most frequent lesion was calcific stenosis of the aortic valve. Of 513 cases of coronary heart disease encountered in 6000 consecutive necropsies, Gardner and White [13] found rheumatic valvular involvement in 6% and also noted that the aortic valve was the most frequently damaged.

Mural Thrombosis, Ventricular Aneurysm, and Fibrous Pericarditis: Thrombi within the left ventricular cavity were observed grossly and verified by histologic study, as was the presence of fibrous pericarditis, either generalized or in small localized patches. The diagnosis of ventricular aneurysm was based on the change in external contour of the ventricular wall and not solely on excavation of the myocardium, which might leave a very thin wall but without external bulging. The data regarding these three lesions are presented in Table 3. It is apparent that these

TABLE 3.—*Data Regarding Mural Thrombosis, Ventricular Aneurysm, and Fibrous Pericarditis*

	Mural Thrombosis (54 Cases)		Ventricular Aneurysm (22 Cases)		Fibrous Pericarditis (35 Cases)	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Cardiac death	44	81	17	77	27	77
Noncardiac death	10	19	5	23	8	23
Av. size of scar, index	54	--	63	--	53	--
Hypertrophy, per cent (av.)	--	80	--	80	--	75
Type of infarct Transmural	39	72	21	95	29	83
Subendocardial	15	28	1	5	6	17
Location of infarct Anterior	41	76	17	77	28	80
Posterior	11	20	5	23	6	17
Lateral	2	4	--	--	1	3

lesions were associated with cardiac death in a considerably higher percentage of cases than they were associated with noncardiac deaths. In addition, they were commonly found in hearts that were markedly hypertrophied and had the largest scars. These scars were usually transmural in extent and were commonly located in the anterior half of the left ventricle. The common association of left ventricular mural thrombosis with anterior infarction, infarcts of large size, and myocardial hypertrophy has been reported by Jordan and associates.[14]

Clinical Features and Cause of Death.—Presence of Hypertension: In this investigation, hypertension was said to be present if the majority of blood pressure recordings on any one patient were more than 150 mm. of mercury systolic and 90 mm. diastolic. Those instances in which a single or a few blood pressure values were slightly elevated were regarded as being unsuited for definite classification. The patients designated as nonhypertensive had an adequate period in which the blood pressure was observed before and after myocardial infarction.

Hypertension was present in 44% of cases, not present in 37%, and not definitely known to be present in 19%. Thus, of 202 cases in which data were sufficient for evaluation, hypertension existed in 54%.

It appears that hypertension is only slightly more frequent in those patients who experience cardiac death (47%) than in those who experience noncardiac death (39%). Among the patients dying of cardiac causes the group with the highest incidence of hypertension (61%) consisted of the patients with congestive failure, as contrasted with 41% for the groups in which sudden death and recurrent acute infarction occurred.

Presence of Angina Pectoris: A history characteristic of angina pectoris was sought in each case. Such distress was required to be present prior to one month before death so as not to be confused with pain occurring as a terminal state was reached. This would tend to eliminate pain from acute infarction or preterminal coronary insufficiency. Angina pectoris was definitely present in 98 patients and probably present in 16 others, a total of 114, which represents 46% of the series. No history of angina pectoris was elicited in 121 persons (48%), and in 15 instances (6%) the data were insufficient for evaluation. It should be noted that 83 of the 157 patients (53%) who died of cardiac causes had a positive history of angina pectoris. This contrasts with the category of deaths from noncardiac causes, in which only one-third of the patients had a history of angina.

It was somewhat surprising that only 46% of the patients included in this study gave a history suggestive of angina pectoris, especially since every heart showed evidence of severe coronary disease. This observation has been made by others, who have reported even lower incidences of angina pectoris in such cases.† The anginal syndrome seemed to be a somewhat unfavorable sign, in that 73% of all those who complained of this distress died subsequently of cardiac causes.

Diabetes Mellitus: Clinical diabetes mellitus was present in 35 of the 250 cases (14%). There were 19 men and 16 women, and so the proportion of women was considerably greater than that found for the entire series. A similar observation has been made by other authors,‡ but the increase in the proportion of women is even more pronounced when the sex ratio of the necropsy population is considered. Thus, 1.3% of all female deaths from which those included in our study were selected were in diabetics with old myocardial scars, while the corresponding figure for men was 0.9%. Diabetic patients were found to be somewhat older, with their average age at death being 68 years. The causes of death among the diabetics were primarily of cardiac origin in 25 of the 35 cases (71%). The pathologic anatomy of the hearts of the diabetics was very similar to that present in the entire series, and, in addition, there was no appreciable difference between the two groups in the incidence of hypertension or angina.

Obesity: The criterion of obesity was arbitrarily set as body weight that exceeded by 15 lb. or more the average weight for height and age as listed in Tables IV and IX from the "Medico-Actuarial Mortality Investigation," Vol. 1.[21] Ninety patients (40% of those on whom data were adequate) were classed as obese, and 134, as not obese, while 26 patients could not be classed because data were inadequate. Of those patients who died from cardiac causes, 63 were obese (45% of those with adequate records), while of those who died of noncardiac causes 27 were overweight (32%). Thus, there appeared to be a tendency for those dying of cardiac causes to be more obese than those dying of noncardiac causes. It is realized that much of these data cover only a short period of the patient's life, so that it is difficult to state what influence, if any, obesity had in the production of coronary sclerosis.

Diagnosis of Previous Myocardial Infarction.—Diagnosis Before Death: The antemortem diagnosis of a previous myocardial infarction had been made with certainty by the clinical observers in 78

† References 7, 9, 15, and 16.

‡ References 5 and 17-20.

cases of this series. From further review of the records and electrocardiograms the diagnosis and date of a previous acute infarction could be established in 30 additional cases. Thus, knowledge of a previous myocardial infarction existed clinically in 108 cases, or in 43% of the 250 cases in the series. In 15 cases the circumstances under which the examination was carried out precluded an adequate evaluation of the cardiovascular status. After exclusion of these cases there were 127 cases in which the occurrence of a previous myocardial infarction was unsuspected prior to death. In eight of these the diagnosis was coronary disease without known myocardial infarction. After the elimination of these 8 cases there still remained 119 cases (48%) in which the presence of severe coronary sclerosis was not recognized prior to the terminal illness, a period arbitrarily defined as one month prior to death. Consequently, the subject of the following comment is these 227 cases, in 108 of which the previous infarction was positively diagnosed before death and in 119 of which it was unrecognized before death.

Surprisingly, a positive antemortem diagnosis of a previous myocardial infarction was made in only 20% of the patients with diabetes as compared with a positive diagnosis in 43% of the entire series. This finding is even more emphasized when it is pointed out that all diabetic patients at the clinic are specifically questioned regarding symptoms of coronary disease by several examiners. Such an observation suggests that in persons with diabetes and coronary arteriosclerosis there frequently may exist a disturbance of the mechanisms of cardiac pain. Such a disturbance could result from some defect in the sympathetic nervous system, for a variety of visceral neuropathies have been observed in diabetic patients. This apparently low incidence of clinically recognized myocardial infarction among patients with diabetes has been noted by others [22] but deserves more thorough study.

It was found that nearly half of all patients who experienced cardiac death had a positive antemortem diagnosis of prior myocardial infarction, as compared with 32% who had such a diagnosis among those dying of noncardiac causes. It would appear that there were more signs and symptoms calling attention to the cardiac status in those patients who subsequently died primarily of their heart disease.

Clinical Diagnosis and Relation to Size, Extent and Position of Scar: The average index of the size of the scar for the 108 cases in which a previous acute infarction was diagnosed clinically was 42 as compared with 29 for the 119 cases in which it was undiagnosed clinically and with 34 for the entire series. This suggests that the larger the site of myocardial scarring the greater is the likelihood of a correct clinical diagnosis. This is further supported by data on scarring involving the ventricular wall; thus, 65% of all transmural infarcts were associated with a positive clinical diagnosis of previous myocardial infarction, while only 35% of the subendocardial scars were so associated. The location of the scar also seemed to have some influence as to whether a correct antemortem diagnosis was made; thus, 58% of the anterior scars, 44% of the posterior scars, and only 26% of the lateral scars were diagnosed before death. However, the anterior scars were considerably larger, on the average, than were those in other locations, and they more frequently involved the myocardium transmurally. As has just been stated, the size of the scar was a factor in diagnosis, so that from the data obtained it cannot be said with certainty that location of the infarction was a separate factor in promoting clinical recognition, although infarcts of the lateral wall are difficult to diagnose even with adequate electrocardiographic exploration.§ In summary, from the standpoint of pathologic anatomy, the ideal myocardial scar for cor-

§ Dunn, W. J.; Edwards, J. E., and Pruitt, R. D.: The Electrocardiogram in Infarction of the Lateral Wall of the Left Ventricle: Clinicopathologic Study, unpublished data.

rect clinical diagnosis was one that was large, that extended transmurally, and that was located in the anterior half of the left ventricle.

Since only hearts with rather large scars were included in this study, it was most surprising to find that in more than half of the patients the infarction was not diagnosed before death, despite adequate opportunity for complete examination. This problem is the subject of continuing investigation.

An unavoidable conclusion is that the clinical recognition of a previous myocardial infarction is difficult in many patients who are seen for general examination or because of other complaints but who are not observed during an acute episode. This remains true despite improved knowledge regarding heart disease and necessitates more careful appraisal of all patients in whom the presence of coronary sclerosis is at all likely.

Length of Survival After Infarction.—The 108 patients who were clinically recognized as having sustained a previous myocardial infarction survived an average of 43 months after that infarction (Fig. 3).

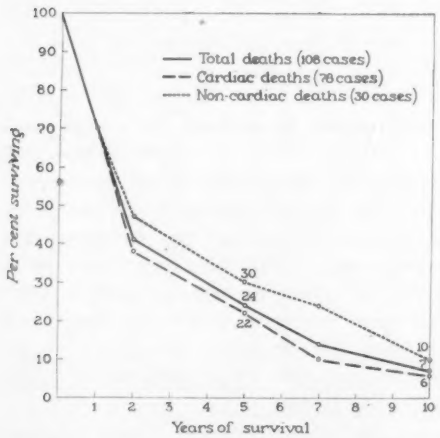

Fig. 3.—Length of survival after recovery from acute myocardial infarction.

The highest mortality occurred in the first two years after the infarction, and this is in agreement with most writers as to the period of gravest risk following recovery from the acute attack. The incidence of survival in the group of cardiac deaths was not significantly different from that in the group of noncardiac deaths. When the cardiac deaths were separated as to sex the survival curves were also very similar.

The average age at death for the entire group of 108 patients in which the previous infarction was diagnosed clinically was 63 years; for those dying of cardiac causes the average age was 62 years, as compared with 67 years for those dying of noncardiac causes. The average age for men at the time of death was 61½ years as contrasted with 71 years for women in that group of patients dying of cardiac causes.

The data from the present study are in general agreement with others || who report a rather unfavorable life expectancy after recovery from myocardial infarction. There were two instances of long survival among our patients. One was a man who lived more than 23 years after an established episode of acute myocardial infarction. The other was a woman who survived 24 years after an illness that was most suggestive of myocardial infarction.

No attempt was made to assess the value of anticoagulant therapy during the phase of acute infarction, since most of the patients had experienced their acute attack prior to the widespread use of such therapy. It was noted, however, that 20 of the 108 patients whose attack was recognizable clinically received anticoagulants during the infarction, which they survived by at least one month. Their average duration of life after this was 18 months as contrasted with 43 months for the entire 108 patients. In addition, nearly one third of the patients who died during a period of recurrent myocardial infarction had received anticoagulants. Since our cases were all derived from a necropsy series and because only a minority of the patients received anticoagulants, no valid conclusions can be drawn regarding the usefulness of such agents.

|| References 8, 9, and 23-25.

Patients Surviving Five Years or More.—The 26 patients who survived five years or longer (24% of those with a positive antemortem diagnosis of previous myocardial infarction), when compared with the entire series from the standpoint of morphologic and clinical findings, revealed no marked differences (Table 4). It is evident from this comparison that few favorable factors of cardiac morphology or clinical examination existed in the the group of patients who had the greatest longevity.

TABLE 4.—*Comparison of Patients Surviving Five Years or Longer After Myocardial Infarction with the Entire 250 Patients in the Series*

Subject for Comparison	5 Yr. Survivals (26 Cases)		Entire Series (250 Cases)	
	Cases	Per Cent	Cases	Per Cent
Sex distribution				
Males	21	81	192	77
Females	5	19	58	23
Age at death, Yr.				
20–49	1	4	23	9
50–59	6	23	58	23
60–69	5	19	80	32
70–79	9	35	62	25
80–100	5	19	27	11
Av. age	69	..	65	..
Cause of death, cardiac				
Congestive failure	6	23	44	18
"Sudden death"	7	27	64	26
Acute infarction	4	15	49	20
Total	17	65	157	63
Cause of death, noncardiac	9	35	93	37
Location of infarct				
Anterior	17	65	116	46
Posterior	7	27	94	38
Lateral	1	4	34	14
Septal	1	4	6	2
Type of infarct				
Transmural	16	62	105	42
Subendocardial	10	38	145	58
Size of infarct (index)	44	..	34	..
Cardiac hypertrophy, av. per cent	..	71	..	60
Valvular lesions	1	4	20	8
Mural thrombosis	9	35	54	22
Ventricular aneurysm	4	15	22	9
Pericarditis	9	35	35	14
Hypertension				
Present	14	54	109	44
Absent	11	42	93	37
Undetermined	1	4	48	19
Angina pectoris				
Present	14	54	114	46
Absent	11	42	121	48
Undetermined	1	4	15	6
Diabetes mellitus	3	12	35	14
Obesity	7	27	90	36
Average survival (108 cases), mo.	113	..	43	..

Consequently, one is led to the conclusion that there are few data that can be used to assist in predicting the subsequent course of individual patients who have survived an episode of acute myocardial infarction.

Summary

Two hundred fifty hearts with gross myocardial scars indicative of healed infarction were selected from necropsies performed at the Mayo Clinic during the five-year period 1946 through 1950 and studied with regard to the pathologic anatomy and its correlation with the clinical features.

The cause of death was primarily of cardiac origin in nearly two-thirds of the patients. There were three major types of cardiac death, namely, death from congestive heart failure, death from recurrent acute myocardial infarction, and "sudden death" without congestive failure or acute infarction. The last-mentioned mechanism was the commonest of the three and was infrequently associated with recent coronary thrombosis.

Antemortem diagnosis of a previous acute myocardial infarction was not made in nearly half of these patients. There appeared to be a definite relationship between the size of the scar indicating the extent of infarction of the ventricular wall on the one hand and the incidence of clinical recognition on the other.

For the patients whose acute myocardial infarction was diagnosed clinically the average length of survival following recovery from the acute episode was 43 months. Only 24% of these patients survived 5 years or more, and only 7% survived 10 years or longer. The period of highest mortality was within the first year after the acute illness.

From the standpoint of cardiac morphology and clinical features the patients surviving five years or longer did not differ significantly from those of the entire series. Hence, it was concluded that the subsequent course of patients who had survived an episode of acute myocardial infarction could not be accurately predicted on the basis of morphologic or clinical findings.

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The Occurrence of Thyroid Nodules in the General Population

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Much confusion exists regarding the management of nodular goiters. The problem which confronts the clinician is whether to surgically remove asymptomatic thyroid nodules solely because of their possible malignancy. The statistics derived from series of surgically treated glands indicate a significant percentage of cancers in both clinically uninodular and clinically multinodular nontoxic goiters.[1] As long as surgeons continue to be presented with the same selection of nodular goiters as has been responsible for these statistics, surgery for such goiters seems indicated. It has been pointed out that these data represent the findings in a selected group of nodular goiters, the selection having been performed by the patient himself, the family physician, and surgeon.[2] The unanswered question at present is what is the frequency of carcinoma in unselected nodular goiters. Sokal [3] and others have suggested that the percentage of malignancies in an unselected group of nodular goiters would be very much smaller than the figures derived from surgical studies. If this is true, it might alter the advice given by the physician to a patient with a nodular goiter which is asymptomatic or symptomatic only because the patient is aware of its existence.

Information as to the incidence of nodular goiter in the general population is needed to evaluate the frequency of malignancies in such goiters. We have had an opportunity to gather such data, and it is the purpose of this report to present these data and some associated findings.

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Methods

The subjects of this study were 1249 patients, 6 years of age and over, cared for on a panel of a prepaid insurance plan. Most of the patients were originally seen for routine physical examinations or for minor illnesses and injuries. No patients cared for by other physicans, and referred for evaluation of their thyroid status, are included in this series. All patients seen from April, 1952, until July, 1955, had their thyroid area palpated, regardless of the presenting complaint, if any. Many of these patients were examined on a number of occasions. All of the subjects included were examined at least once by the same observer. In almost every patient with abnormal palpatory findings of the thyroid gland, the findings were confirmed by a second observer. Corroboration was not obtained in only the few patients who refused to be examined by a second physician. None of the subjects noted by us to have a non-nodular gland have been found to have a nodular goiter when subsequently examined by another physician.

Some of the subjects in the series had had a thyroidectomy performed prior to being seen initially by us. In these instances, knowledge of the previous clinical and pathological nature of the thyroid gland was obtained from the former attending physician or from the hospital where surgery was performed. Pathological data were obtained for those in the series operated upon after our discovery of the nodule. Radioactive iodine studies were done whenever possible.

Results

The age and sex distribution of the examined persons is presented in Table 1 and is compared with the age and sex distribution

TABLE 1.—*Population Distribution by Age and Sex*

Age, Yr.	U.S.A. Population		Medical Group		Series Studies	
	% Male	% Female	% Male	% Female	% Male	% Female
6 — 9	5.8	5.5	4.4	4.5	7.0	4.2
10 — 19	8.4	8.1	7.8	7.1	8.3	8.4
20 — 29	7.8	7.9	7.2	9.2	5.8	7.5
30 — 39	8.1	8.4	12.5	11.1	14.0	10.5
40 — 49	7.2	7.3	9.9	8.9	8.5	7.9
50 — 59	5.6	5.8	6.8	5.7	7.4	5.9
60 — 69	4.0	4.2	2.8	1.6	2.7	1.2
70 and over	2.7	3.2	0.4	0.1	0.5	0.2
TOTAL	100		100		100	

TABLE 2.—*Clinical and Laboratory Data in Patients with Nodules*

Patient	Age, Yr.	Parity	Reason for Establishment of Doctor-Patient Relation	Physical Character of Thyroid Gland	Isotopic Nature of Nodule	Remarks
1.	32	+	Sprained ankle	1 cm. solitary nodule, right lobe	Cold	Nodule known to be present 4 yr.
2.	46	0	Angina	Not enlarged; multiple small nodules		
3.*	29	+		Single nodule		Pathologically benign
4.	49	0	Upper respiratory infection	Three times normal size; multinodular		Presence of goiter known for years
5.	35	Male	Check-up	3 mm. solitary nodule in isthmus		
6.	37	+	Upper respiratory infection	1.5 cm. nodule, right lobe	Hot	Nodule did not change after administration of thyroid 260 mg. q.d. for 2 mo.; pathologically benign single nodule, 1.8 cm.
7.	34	+	Anxiety state	1½ times normal size, multinodular		
8.	37	0	Upper respiratory infection	1.5 cm. solitary nodule, left lobe	Cold	Pathologically benign solitary nodule
9.*	35	+	Solitary nodule	Solitary nodule		Operated upon 15 years previously; pathology report unavailable
10.*	44	+	Routine examination	Solitary nodule		Pathologically single and benign
11.	37	Male	Hypoadrenocorticism	Minimally enlarged, multinodular		
12.	54	Male	Hernia	Solitary nodule, left lobe		Unchanged after 3 yr. observation
13.*	48	+		Solitary nodule, right lobe		Pathologically single and benign
14.	45	+	Anxiety state	Slightly enlarged, multinodular		
15.	39	+	Anxiety state	1½ times normal size, multinodular		Pathologically benign and multinodular
16.*	33	0		Single nodule		Removed in 1940; pathologically benign and single
17.	55	0	Check-up	Solitary 1 cm. nodule, left lobe		Pathologically benign and single; 2 cm.
18.	45	+	Anemia	Solitary 2×3 cm. nodule, left lobe	Cold	Pathologically single and carcinoma; 2.5×3.5 cm.
19.	63	+	Pedal edema	1 cm. solitary nodule in pyramidal lobe	Cold	
20.	46	+	Sprained ankle	Slightly enlarged, multinodular		
21.*	35	+		Multinodular		Pathologically benign and multinodular
22.	46	0	Cirrhosis and alcoholism	2 cm. solitary nodule, right lobe	Hot	May have been toxic
23.	62	Male	Upper respiratory infection	1 cm. solitary nodule, left lobe		
24.	30	+	Upper respiratory infection	5-6 mm. solitary nodule, right lobe	Hot	Nodule did not change after 3 mo. thyroid 260 mg. q.d.
25.	38	+	Anxiety state	Slightly enlarged, multinodular		
26.*	51	Male		Multinodular gland, toxic		Benign, multinodular
27.	45	+	Asthenia	1 cm. solitary nodule in isthmus	Hot	Nodule did not change after 3 mo. thyroid 260 mg. q.d.; pathologically benign and solitary
28.	55	+	Tinnitus	3 times normal size, multinodular		
29.	55	+	Check-up	1.5 cm. solitary nodule, left lobe		Present for 4 yr.
30.	66	0	Diabetes mellitus	Normal size, multinodular		
31.	39	Male	Check-up	1×1.5 cm. solitary nodule, left lobe	Cold	
32.	33	+	Sinusitis	2 cm. solitary nodule, right lobe		

* Thyroidectomy performed prior to our original examination.

TABLE 3.—*Occurrence of Nodules in Relation to Age and Sex*

Age, Yr.	Males	Females			Total
		Pre-menstrual	Nulli-parous	Parous	
6-9	0/0*	0/0	---	---	0/0
	87	52			139
10-19	0/0	0/0	0/0	---	0/0
	104	44	61		209
20-29	0/0	---	0/0	0/1	0/1
	72		27	67	166
30-39	1/2	---	0/2	4/5	5/9
	175		13	118	306
40-49	0/0	---	3/1	1/4	4/5
	106		16	83	205
50-59	1/1	---	0/1	1/1	2/3
	92		17	57	166
60-69	0/1	---	1/0	0/1	1/2
	34		1	14	49
70 and over	0/0	---	---	0/0	0/0
	6			3	9
Total	2/4	0/0	4/4	6/12	12/20
	676	96	135	342	1249

* $\frac{a/b:}{c}$ *a*, number of multinodular goiters; *b*, number of uninodular goiters; *c*, number of patients examined.

of the entire insured population in the medical group as of July, 1954, and with the population distribution for the U. S. as estimated as of July, 1954 (in all cases, excluding persons less than 6 years of age.) There is no statistically significant difference among various groups ($P>0.1$). In Table 2 are listed the pertinent available data for those persons found to have, or to have had, a nodular goiter. In Table 3 the group of examined patients is divided according to age and sex, and the number of patients in each group with uninodular and multinodular goiters is indicated. The ages given are those at which the nodule was originally discovered. The female patients in the series have been divided into three groups: the premenstrual, the postmenarchal nulliparous, and the parous. Not included in the data are two males with thyroglossal cysts, which were removed at the ages of 4 and 9 years, respectively. No other thyroglossal cysts were found. Excluded also is one woman who had had a thyroidectomy many years before and for whom the type of goiter and pathological findings could not be ascertained.

Nodular goiters were detected by us in 25 patients. In seven additional persons a nodular goiter had been removed prior to our original examination. Thus, the overall incidence of nodules in the thyroid gland in this series was 2.6%. Clinically solitary nodules were found in 1.6% of the subjects and 1.0% had multinodular glands. The greater frequency of solitary nodules is in keeping with the findings of Vander and associates,[4] which were obtained in an unselected population group composed of persons 30 through 59 years of age residing in New England. In addition, they noted a total incidence of nodular goiters of 4.0% in this age group; when the present data are calculated to include only these age groups, the incidence of nodular goiter is found to be 4.1%.

The greater frequency of nodular goiters in women is noted, 4.5% of the women in this series having a nodular goiter as compared with only 0.9% of the men. Among the reasons given for the increased frequency of adenomatous goiter in women are the stresses attendent upon menstruation, pregnancy, and the menopause.[5] The absence of nodules in the premenstrual group would be harmonious with this proposition. The incidence of nodules is almost the same, however, in those women who have never been pregnant (5.9%), and in those who have had one or more pregnancies (5.3%), which is not what one would expect if pregnancy was a causative stress.

Most of the persons examined were lifelong residents of the New York area, and, so far as could be ascertained, none of the others had lived in an endemic goiter region. All of the patients were euthyroid at the time of examination. The sole exception to this may have been Subject 22, but a final evaluation could not be made because of lack of cooperation. One of the males with a previously removed multinodular goiter had undoubtedly been toxic. One of

the women with a previously removed uninodular goiter may have been toxic but probably was not. No dietary idiosyncrasies were elicited.

In the course of reexamination of many of the persons in the series, only one was found in whom a nodule definitely developed under observation. The patient, Subject 24, was originally seen in May, 1953, for rheumatic heart disease complicated by auricular fibrillation with a ventricular rate which was difficult to control. Because of the reported high incidence of hyperthyroidism in association with auricular fibrillation, the thyroid gland was carefully examined, and no abnormalities were noted. When the patient was seen again, in September, 1954, for an upper respiratory infection, a questionable 3 mm. nodule was noted in the lower pole of the right lobe of the thyroid gland. When she was seen again, in April, 1955, it was noted, prior to reference to the record of September, 1954, that a nodule, estimated to be 5 to 6 mm. in size, was present in the lower pole of the right lobe. The presence of the nodule has been confirmed by other observers; in addition, when the thyroid area was scanned after a tracer dose of radioiodine a localized area of hyperactivity was found over the site of the nodule.

Of the solitary nodules tested with directional counting after the ingestion of a dose of radioiodine, five were "cold" and four were "hot." (A "hot" nodule is one which concentrates more radioiodine than the non-nodular portion of the gland, and a "cold" nodule is one which concentrates only as much, or less.[6]) Three of the subjects with "hot" nodules were treated with thyroid extract, with no alteration of the physical findings of the nodules.

Five person with uninodular glands and two with multinodular glands had been operated upon prior to coming under our observation. Except for one uninodular gland for which the pathological data are unavailable, the gland in each case was pathologically benign. No further symptoms or signs referable to the thyroid gland have been noted in any of these persons. Five persons with uninodular goiters and one with a multinodular goiter were operated upon after coming under our observation. All these goiters were clinically benign. Of these, only one gland, a uninodular one, was pathologically malignant. The latter patient is alive and well two and a half years after hemithyroidectomy and x-ray therapy. In each instance, the preoperative estimate of the number of nodules was in agreement with the surgical and pathological findings.

Comment

The close agreement of our findings with those of Vander's unselected group has been noted above. It is felt that the persons examined by us closely approach an unselected group. Since the cost of medical care to the subjects is not dependent upon the number of professional services received, many of them would be expected to seek medical advice for a check-up or for minor complaints. This is borne out by the presenting complaints (Table 2). If any selection is present, it is toward the younger age groups and the male sex, which would tend to make the over-all incidence of nodules lower than in a population group with no selection at all.

The clinically determined prevalence of nodules noted by Vander and associates and by us is considerably less than that noted in studies done on thyroid glands obtained from routine necropsies. Hellwig[7] has reported the occurrence of thyroid nodules in 51% of necropsies. Hazard and Kaufman[8] noted the presence of thyroid nodules in 42.4% of the glands examined, and Hull,[9] in 64%. Mortensen and associates[10] found 49.5% of the glands which they examined to contain nodules. If the available autopsy data are analyzed, accepting 1 cm. as the size of the smallest nodule which would be clinically palpable, the incidence of clinically palpable nodular goiter would be 7% in adults in Kansas,[7] 8% in adults in the Boston area,[11] and 12% in adults aged 30 to 59 years in the Colorado area.[9]

There are probably several reasons for the discrepancy noted between the clinical and autopsy findings. One factor is the differences in the composition of groups studied. The necropsy series usually are composed of an increased percentage of older subjects, in whom the incidence of nodules is usually higher. Hellwig [7] and Hazard and Kaufman [8] studied persons from endemic goiter areas. The differences in frequency of thyroid nodules noted by Schlesinger and associates [11] among the several hospitals from which their statistics are derived may reflect differences in the geographic origin of the persons autopsied. In addition to whatever differences in sample may exist between the clinical and autopsy studies, there are certain factors inherent in the clinical examination of a thyroid gland which will result in the detection of a smaller number of nodules than actually exist. These factors may be divided into thyroidal and extrathyroidal.

The extrathyroidal element is obvious: In order to detect the presence of a nodule in the thyroid gland, one must be able to palpate the gland. In persons with a short thick neck the thyroid gland is often inaccessible to palpation, or just the superior portion of it can be felt. This difficulty is encountered especially in older persons; the kyphosis which develops in older persons and the hypertrophic changes of the sternoclavicular joints often result in a marked reduction of the area above the suprasternal notch where the thyroid gland is ordinarily palpated. Extending the neck in an attempt to make the gland palpable in these cases is usually an unsuccessful maneuver because the concomitant tightening of the strap muscles prevents satisfactory palpation. In obese patients the interposition of a mass of tissue between the skin and the thyroid gland renders palpation difficult. A certain number of nodules which may be undetected clinically because of these factors will, of course, be discovered with ease by the autopsy pathologist.

Even when the thyroid gland is accessible to palpation, there are several intrinsic factors which contribute to the clinicians' fallibility in distinguishing a nodule from surrounding normal thyroid tissue. Mortensen and associates [10] have noted that these factors render palpation of the intact thyroid gland unreliable even after the gland has been removed at necropsy and before it has been sectioned. These factors are the consistency of the nodule, its size, and its location. The less a nodule differs in conmore superficially located in the thyroid gland, the more difficult it is to appreciate it as a nodule and the larger must it be to be distinguished. A nodule which is more superficially located in the thyroid gland can be more easily palpated than one more deeply situated, and the larger the thyroid gland the more difficult it is to feel a deeply situated nodule of a given size. Finally, a nodule must be of a certain minimal size before the clinician can be certain of its existence. In a number of persons examined, a fine nodularity of the thyroid gland seemed to be present, but the minimal palpatory changes precluded our being certain of the existence of the nodule or nodules, and such glands have been considered to be non-nodular. Undoubtedly some of these glands would correspond to the glands noted by the pathologist as containing very small nodules. These factors, with which the pathologist does not have to contend, would account for some of the discrepancy noted between the clinical and autopsy findings.

In trying to decide which nodules found at necropsy might have been palpable clinically, it has been assumed by previous authors that a nodule of 1 cm., as measured by the pathologist, is the smallest one which might have been palpated. In the few cases in this series where the preoperative estimate of the size of the nodule and the size as determined on the resected specimen are available, it can be seen (Table 2) that the size was underestimated preoperatively by 0.3 to 1.0 cm. This would indicate that a nodule must be more than 3 ml. in size to be palpable clinically, and probably larger. One nodule, not included in this series,

was agreed preoperatively by three observers to be 3 to 4 ml. in diameter; when resected and sectioned, it was found to be 1 cm. in diameter.

Summary

The occurrence of thyroid nodules in a sample of the general population was studied. The frequency of uninodular and multinodular goiters in various age-sex groups is presented with related clinical and pathological data. The findings are compared with previous data available in the literature.

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Study in the Controlled Therapy of Degenerative Arthritis

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Upon organizing a clinic for the study and treatment of joint disease in the Cook County Hospital, we were confronted by an unlimited number of patients. As treatment we had liberal hospital facilities and provision for physical medicine.

A galaxy of drugs was available, some of these dignified by long use. Others had been recently introduced, were widely used, and were currently accepted with considerable enthusiasm. Some of the new chemicals, offered to us for clinical trial after preliminary laboratory evaluation, were possibly harmful and only questionably beneficial. The skeletal disease in most of our patients was chronic and rather stationary, with an unmeasured tendency to spontaneous remissions and relapses. Most of the patients had tried many drugs and procedures upon the advice of physicians, drug stores, advertisements, or acquaintances. Almost all the patients had taken acetylsalicylic acid or proprietaries containing salicylates. The application for help in our clinic could be taken as evidence of the absolute or relative ineffectiveness of their previous therapeutic adventures.

To care for our patients intelligently and effectively and to utilize the tremendous clinical opportunities of separating the grain from the chaff, controls were set up for the evaluation of treatment.

Factors other than therapeutic had to be considered as favorably influencing the course of the disease, thus tending to becloud evaluation of treatment. A subtle source of error in appraisal of treatment results is the natural history of the sickness, the fluctuating influences of the harmful agent, and of the body's defense.

The placebo factor in all contacts between healer and patient and the reaction of the patient to sympathetic interest required evaluation in order to determine the best interests of the patient regarding continuation, increased or decreased dosage, or even cessation of a given treatment.

Procedure

Every patient entering the clinic gave a complete medical history and was thoroughly examined. While awaiting the results of the laboratory tests and during the week intervening before his next clinic visit, he was told to take a white tablet containing 5 grains (0.3 gm.) of lactose after meals and on retiring. At his next visit he was asked, "How are you?" No leading question, hopeful inflection of the voice, or confident smile accompanied the query. The patient's reply was entered verbatim. A patient noting some change, good or bad, was asked to particularize and demonstrate evidence of any alteration of swelling, mobility, or tenderness. Sedimentation-rate determination (Westergren) and other laboratory tests were performed at the first visit and frequently thereafter. Care was taken to give no other therapeutic advice, such as change of diet, correction of posture, application of heat, or change in working habits. The patient was also told to avoid acetylsalicylic acid and any other medica-

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From the Arthritis Clinic of the Cook County Hospital and from Presbyterian Hospital.

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tion or therapeutic procedure. The patient's course was observed by six attending physicians of the Arthritis Clinic. He was told to return in one week to report on his condition and to be examined.

With a report of improvement, even slight, the lactose tablets were continued. A given procedure was not changed until improvement in symptoms, or in symptoms and findings, ceased. Patients reporting an equivocal improvement in some nonskeletal system were classified as unimproved.

If the patient reported no improvement or a worsening, the lactose was discontinued and the patient was given a subcutaneous injection of 1 cc. of isotonic saline solution.

Obviously, a patient responding favorably, as evidenced by continued improvement or persistent remission to either placebo, would be unsuitable for evaluation of any potentially active drug or other therapeutic procedure. A patient progressively improving was allowed to remain on placebo indefinitely. In a few instances attempts were made to "gild the lily" by replacing the placebo for a period of weeks by salicylates, cortisone, or phenylbutazone. In some instances of remission induced by salicylates, cortisone, phenylbutazone, or other procedure the antirheumatic principle was stopped and a placebo substituted. The remission would sometimes continue under the placebo procedure.

The few patients not returning after their first visit and prescription for placebo tablets were omitted from our study. We found the chief causes for failure to return to the clinic to be disappointment due to lack of prompt relief or to resentment at the required laboratory precedures, change in residence, or an intercurrent illness, such as a cold. Marked remissions immediately following the first clinic visits almost balanced the disappointments as reasons for not returning to clinic.

Most patients with skeletal complaints are over 35 years old; have symptoms in the large, weight-bearing joints; are usually female and over-weight; have postural abnormalities, and frequently show osteophytes about the ends of the bones. This group is classified as having degenerative or hypertrophic arthritis, arthrosis, or osteoarthritis. This report describes our experiences with placebo treatment of patients with degenerative arthritis.

Results in Degenerative Arthritis

One hundred-eighty-two patients (Table 1) with degenerative arthritis received placebo tablets from 4 weeks to 26 months.

TABLE 1.—*Degenerative Arthritis: Results with Placebo Tablets*

No. of Patients	Duration of Therapy, Wk.	Improvement		
		None	Moderate	Marked
107	4 or less	56 52%	28	23
			48%	
27	8	12	4	11
7	12	2 28.5%	3	2
			71%	
30	16–32	4	5	21
11	52–104	0	1	10
Total 182	1–104	74 41%	41	67
			59%	

Fifty-nine per cent were improved. Fifty-nine per cent (over half) of the patients took placebo tablets only one month. In more than half (52%) of these patients receiving the tablets four weeks or less the placebo tablets were ineffective, accounting for the relatively short period of their admisistration. Only 48% of those taking placebo tablets for one month were improved. This discrepancy between patients taking the tablets for a short and for a long time reflects the number of patients at first found suggestible but in whom the initial suggestion lost its primary benefit.

This first group of failures includes patients who are not only "placebo resistors" but many who resist all forms of medication, including drugs known to be pharmacologically effective in many patients (such as salicylates and phenylbutazone), but also a few who claim no relief from such definite analgesics as codein or morphine. Some of these latter may be aware of the placebo study and insist that the usually effective analgesic is only the placebo tablet. The relatively large number (37) of patients benefited continuously or progressively for six months or more includes a few failures after this long period of placebo tablets, some patients entirely relieved, and others enough relieved to justify discontinuing their clinic visits.

As anticipated, placebo tablets were of

most benefit in patients with the mildest degree of degenerative arthritis (Table 2).

TABLE 2.—*Degenerative Arthritis: Results with Placebo Tablets; Ratio of Severity to Improvement*

Severity of Arthritis	No. of Patients	Improvement		
		None	Moderate	Marked
Mild	108	36 33%	26	46 66%
Moderate	62	32 52%	12	18 48%
Severe	12	6 50%	3	3 50%
Total	182	74 41%	41	67 59%

Most of the failures were in patients with the severest complaints and findings. This tendency of the patients with less severe forms of disease to show the most improvement is common to all forms of treatment and all kinds of diseases. The over-all balance again demonstrated placebo tablets to be effective medication in most (59%) of the patients with degenerative arthritis.

Coincidentally with the decreased pain came increased motion of involved joints. Decrease in the swelling followed. As with other medicines we have had patients initially benefited relapse while taking placebo medication. Patients often reported lessening of symptoms within minutes or hours after swallowing a placebo tablet and immediate relapse on ceasing to take the tablets. About one-half of the patients initially relieved by placebo tablets later complained that the tablets did not help them. It was usually not possible to reinduce the placebo effect either by increasing the number of tablets or the frequency of their administration. The elevated sedimentation rate found in a few of these patients with degenerative arthritis was attributed to traumatic synovitis. Placebo therapy had no constant effect upon the accelerated sedimentation.

Patients receiving placebo often volunteered that they slept better, their bowels moved more regularly, or their heads felt clearer. On the other hand, some complained of ringing in the ears or nausea similar to that induced by acetylsalicylic acid. Such are good and bad side-effects of placebo medication exactly reproducing experiences of patients taking other pharmaceuticals.

More women than men were benefited. The percentage of Negro patients responding to placebo tablets was only slightly greater than the percentage of white patients (Table 3). The Negroes also responded quantitatively more intensively than the white patients.

TABLE 3.—*Degenerative Arthritis: Results with Placebo Tablets; More Women than Men were Benefited; Negro Patients Responded to Placebos with More Benefit than Whites*

Sex	Race	No. of Patients	Improvement		
			None	Moderate	Marked
Male	W	47	25 53%	9	13 47%
	N	27	12 44%	8	7 56%
Female	W	46	17 37%	12	17 63%
	N	62	20 32%	12	30 68%
Total		182	74 41%	41	67 59%

Seventy-seven patients with degenerative arthritis not improving with placebo tablets were given subcutaneous injections of saline solution.

This group included patients initially not responsive to placebo tablets as well as patients immediately improved by placebo tablets but later relapsing while taking placebo tablets. The response (Table 4) to the injected placebo practically duplicates the percentage improved by placebo tablets. This is the more remarkable, since this group, composed of patients found initially to resist the placebo effect of tablets and of patients having ceased to be relieved by

TABLE 4.—*Degenerative Arthritis: Results with Placebo Saline Injections; Approximately Same Percentage of Total Cases Improved as Was Benefited by Tablets; This Group Treated at First by Tablets, Later by Injection*

No. of Patients	Duration of Therapy Wk.	Improvement		
		None	Moderate	Marked
36	4 or less	27 75%	5	4 25%
11	8	3 27%	4	4 73%
9	12	3 33%	1	5 66%
13	16-23		7	6
8	52-112			8
Total 77		33 43%	17	27 57%

placebo tablets, might be assumed to contain a high percentage of placebo resistors.

Again, the largest number of placebo failures were those receiving injections for the shortest time (four weeks or less). This group includes patients most markedly resistant to placebo: those who were found unaffected to placebo tablets and were immediately (on second visit) given hypodermic injection of isotonic saline solution.

As with the placebo tablets, the patients least encumbered with arthritis were helped most by injected placebo (Table 5). The number of severely ill patients treated with either tablets or injections is statistically unimpressive.

TABLE 5.—*Degenerative Arthritis: Results with Placebo Saline Injections; Patients with Less Severe Arthritis Were Most Improved*

Severity of Arthritis	No. of Patients	Improvement		
		None	Moderate	Marked
Mild	39	13 33	10	16 67%
Moderate	33	19 57½	5	9 42½
Severe	5	1 20%		4 80%
Total	77	33 43%	15	29 57%

"Improvement" as recorded by us, refers only to lessening of the joint disease. In addition, patients almost regularly volunteered that they slept better, their bowels moved better, they had less headache, or they were stronger.

In some instances the usual procedure of injecting the saline solution under the skin of the arm was changed to place the injection close to or in the affected part. This change in location of the injection often increased the effectiveness of the procedure.

The men not responding to the placebo effect of tablets responded in a higher percentage to placebo injections. There was an unimpressive sex difference. Negroes with degenerative arthritis, both men and women, responded better than whites to saline injections (Table 6).

TABLE 6.—*Degenerative Arthritis: Results with Placebo Saline Injections; The Injections Were More Effective in the Negroes and in Men*

Sex	Race	No. of Patients	Improvement		
			None	Moderate	Marked
Male	W	21	9 43%	4	8 57%
	N	11	4 36%	4	3 64%
Female	W	18	9 50%	1	8 50%
	N	27	11 41%	6	10 59%
Total		77	33 43%	15	29 57%

Comment

The propriety of using placebo medications to control *post hoc* judgments following various procedures used with therapeutic intent is established by respected precedents.* Such a procedure is especially

* References 1-4.

needed in evaluating the treatment of rheumatic syndromes.

Arthritis is almost unique in the number of substances and procedures advanced for its treatment.

In all chronic illness, and especially in rheumatic disorders, the psyche plays an important symptomatic role. Through the psyche, desirable and undesirable effects upon the course of the disease may be enhanced or even induced.[5]

Most of the proposed therapy has given the never-lacking equivocal or placebo-percentage benefit. Sulfur preparations were injected intramuscularly and intravenously within recent memory. Other drugs, such as vitamin D in high dosage and various gold preparations, of dubious value but unquestioned hazard are still being used in some quarters.

It should be more generally appreciated that there is a placebo effect in all treatment of any conscious patient regardless of his complaint or disease. The familiar percentages are apparent in the perennial crop of medicines. This real but definitely placebo improvement observed in all patients with all therapeutic procedures is responsible for the thick pharmacopoeias and books on therapy.

We have found it necessary and desirable to measure the effects of any treatment subjectively as well as objectively according to the more usual criteria applied practically by patients as well as their doctors in estimating the benefit of any procedure used as treatment. Our use of placebo satisfied the patient's anxiety to start treatment. The charting of the patient's suggestibility established the base line portraying how much of the result following any treatment might be adjudged psychic. This is the more desirable since the advent of the currently used "miracle" drugs given as tablets and by injection with a background of combined fanfare, glamor, and promise engendered by articles in lay journals and in radio and television presentations without complete realization of the frequent failures and harmful effects.

We have recently heard a refreshing discussion of the comparative effects of acetylsalicylic acid and cortisone by workers in Britain.[6] These workers might advantageously have utilized some inert substance in tablet form (placebo tablet) and ended up with figures approaching the number of patients benefited by acetylsalicylic acid or cortisone.

Our patients were not harmed by the administration of placebos. Placebo tablets were to be taken during the first week of observation, a time of tests and x-ray studies. The placebo, being neither a uricolytic nor a stress substance, did not interfere with such studies as determination of the uric acid in the serum, the measurement of the sedimentation rate, or the estimation of circulating eosinophiles. If the placebo procedures did not benefit the patient in any manner or ceased to benefit him, the placebo was stopped and other measures instituted.

Summary

Placebo given orally or by injection relined the symptoms and abolished the signs in more than one-half of the patients presenting themselves with degenerative arthritis in a clinic of a metropolitan center. About one-half of the patients were benefited by the placebo tablets or placebo injections for more than one month.

Placebo was most effective in patients showing the less severe types of the disease.

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Drug Therapy (Mecamylamine) of Hypertension

III. Results with Mecamylamine, a Completely Absorbed Ganglionic Blocking Agent

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Ganglionic blocking agents appear to be the most potent therapeutic agents for reducing the blood pressure in patients with severe hypertension. However, the orthostatic effect and the variability in blood pressure response to currently available ganglionic blocking agents are the most serious limiting factors in the use of these agents and may completely prohibit their use in some patients. Concurrent administration of rauwolfia, which depresses the sympathetic nervous system in the brain, partially stabilizes the blood pressure response. However, even then extreme variability frequently exists, apparently due to incomplete and variable absorption of these agents (hexamethonium and pentolinium) from the gastrointestinal tract.*

Recently another long-acting gangionic blocking agent has become available for clinical trial.† This compound, mecamylamine,‡ is a secondary amine (rather than a quaternary compound) which is completely absorbed from the gastrointestinal tract. For this reason it has been investigated as a therapeutic agent for reducing the blood pressure in patients with hypertension. The following report is based on the use of mecamylamine in the treatment of hypertension.

Methods and Materials

This study consisted of a group of 104 patients from the hypertension clinics of the Hermann Hospital, the Jefferson Davis Hospital, the Veteran's Administration Hospital, and the private practice of each of us. The majority of these patients were treated entirely on an outpatient basis. In a few patients with severe disease, such as hypertension associated with encephalopathy and cardiac failure, it was necessary to initiate therapy in the hospital. After therapy was started, these latter patients were then followed as outpatients. All patients had blood pressures as measured in both the supine and the upright position of 150/100 mm. Hg or greater prior to treatment. Control observations were determined by taking the average of a minimum of four separate blood pressure and pulse rate determinations over a one-month period in the supine and upright positions while the patients received a placebo. The observations after drug therapy were the averages of all blood pressures and pulse rates in both the supine and the upright position taken after an effective dose of the drug had been established for each patient, i.e., after the titration period, during which time the blood pressure and drug dosage were being stabilized.

Prior to therapy, all patients were carefully evaluated as to a preliminary history and physical examination, complete blood cell count, electrocardiogram, blood urea nitrogen determination,

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From the Departments of Pharmacology and Medicine, Baylor University College of Medicine, and the Cardiac Clinic of the Jefferson Davis Hospital, the Hermann Hospital, and the Medical Service of the Veteran's Administration Hospital.

* References 1 and 2.

† References 3 and 4.

‡ Available as Inversine from Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

TABLE 1.—*Summary of the Clinical Status and Complications of Patients with Hypertension Prior to Receiving Mecamylamine Alone (Group 1) and Mecamylamine plus Rauwolfia (Group 2)*

	Patients Treated, No.	Average Age, Yr.	Sex		Race		Renal Damage*		Cardiac Failure		Angina Pectoris		Abnormal ECG†		Cerebral Damage		Fundi‡			
			Male	Female	White	Negro											1+ or 2+		3+ or 4+	
							No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Group 1 (patients treated with mecamylamine alone)																				
Subgroup A (control upright diastolic blood pressure >100 mm. Hg but <120 mm. Hg)	10	53	2	8	3	7	5	50	4	40	2	20	8	80	2	20	9	90	0	0
Subgroup B (control upright diastolic blood pressure >120 mm. Hg)	14	58	6	8	2	12	10	71	4	29	4	29	7	50	1	7	9	64	3	21
Total (A & B)	24	56	8	16	5	19	15	63	8	33	6	25	15	63	3	13	18	75	3	13
Group 2 (patients treated with mecamylamine plus rauwolfia)																				
Subgroup A (control upright diastolic blood pressure >100 mm. Hg but <120 mm. Hg)	15	54	3	12	4	11	5	33	5	33	2	13	9	60	0	0	11	73	3	20
Subgroup B (control upright diastolic blood pressure >120 mm. Hg)	65	51	27	38	20	45	44	68	27	42	13	20	44	68	16	25	46	71	19	29
Total (A & B)	80	52	30	50	24	56	49	61	32	40	15	19	53	66	16	20	57	71	22	28
Grand total	104	53	38	66	29	75	64	62	40	38	21	20	68	65	19	18	75	72	25	24

* Varies from proteinuria to fixed specific gravity of the urine and elevated blood urea nitrogen.
† Varies from nonspecific T wave changes to left ventricular hypertrophy.
‡ Keith-Wagener-Barker classification.

chest roentgenogram, urinalysis, and, in some cases, Fishberg concentration test and phenolsulfonphthalein test. In addition to blood pressure and pulse rate, weight, and temperature determinations, a brief history was taken and physical examination was made on each clinic visit after the drugs were started.

In order to determine the blood pressure response, side-effects, drug dosage, and clinical response to therapy with mecamylamine alone as compared with mecamylamine used in combination with rauwolfia, the patients have been divided into two groups. Group 1 consisted of 24 patients who received mecamylamine alone. A larger group, of 80 patients (Group 2), received mecamylamine and rauwolfia § and have been followed for a period of four months or more.

Thirty-five of the eighty patients who received the rauwolfia and mecamylamine in combination for six months or more have been used to compare the effect of time on continued therapy. Therefore, the treatment period of these 35 patients has been subdivided into two consecutive periods of three months each (D_1 and D_2).

Of the 24 patients receiving mecamylamine alone (Group 1), 8 were men and 16 were women. There were 5 white and 19 Negro patients. A summary of clinical status and complications of hypertension prior to their receiving mecamylamine alone is presented in Table 1. Two-thirds of these patients had evidence of renal damage. Cardiac failure was present in one-third, and one-fourth complained of angina. Two-thirds had abnormal electrocardiograms, and 13% had previously diagnosed cerebral vascular accidents. Seventy-five per cent of these patients had 1+ or 2+ retinal changes of hypertensive vascular disease according to Keith-Wagener-Barker Classification, and thirteen per cent had hemorrhages and/or papilledema.

Of the 80 patients receiving mecamylamine plus raufolfia, 30 were men and 50 were women; there were 24 white and 56 Negro patients. A summary of their clinical status and complications of hypertension prior to therapy is presented in Table 1. Renal damage varying from proteinuria to fixed specific gravity and elevated blood urea nitrogen was present in about two-thirds of these patients. Cardiac failure was present in 40%, and 19% experienced angina. Abnormal electrocardiograms varying from nonspecific T wave changes to left ventricular hypertrophy were present in two-thirds of the patients. Only one patient in this group had a previous myocardial infarction. Sixteen (20%) of the patients had cerebral vascular accidents prior to therapy. Of the 80 patients, 79 had the retinal changes of hypertensive vascular disease, and retinal hemorrhages and/or papilledema was present in 28% of the patients.

TABLE 2.—*Method of Dose Titration of Mecamylamine**

	Dose of Mecamylamine, Mg.			
	7 A. M.	12 Noon	5. P. M.	10 P. M.
1st week	2.5	----	2.5	----
2d week	5	----	5	----
3d week	5	5	5	5
4th week	5	10	5	5
5th week	5	10	10	5
6th week	5	15	10	5
7th week	10	15	10	5
Etc.	Etc.	Etc.	Etc.	Etc.

* The dose was maintained at whatever level was accompanied by an adequate reduction in blood pressure.

§ Reserpine, furnished by Ciba Pharmaceutical Products, Inc., as Serpasil and by Eli Lilly & Company as Sandril, and alseroxylon, furnished by Riker Laboratories, Inc., as Rauwiloid.

The 24 patients in Group 1 received mecamylamine only. The initial dose, which rarely produced the side-effect of excessive hypotension, was found to be 2.5 mg. twice a day. This initial dose was gradually increased in a step-wise fashion (Table 2; Fig. 1) until adequate blood pressure response was obtained or until side-reactions necessitated discontinuing therapy or reducing drug dosage, which was sometimes the case. The drug was given after meals to allow a more constant and prolonged absorption. The guide to the weekly changes in dosage was the upright blood pressure as well as the clinical manifestations of excessive hypotension such as weakness and dizziness on standing. Increments in drug dosage were made first in the noon dose and later in the dose after the evening meal. The morning dose was relatively small, and the night dose was also small. In our experience, this method allows a more constant blood pressure response with fewer side-effects. If the patient experienced weakness and dizziness due to excessive blockade when first arising in the morning (before taking medication), the bedtime dose was progressively reduced (and in some cases dropped) until these early morning symptoms were abolished. About one fourth of the patients seemed to do better without using a bedtime dose.

The patients in Group 2 received reserpine (1 mg. daily in divided doses) or alseroxylon (4 mg. daily) for two months or more prior to adding mecamylamine. None of these patients had become normotensive while receiving rauwolfia. When mecamylamine was started in these patients the dose was titrated in a way similar to that used for the patients in Group 1, who received mecamylamine alone.

Results

For purposes of analysis of results the patients have been divided into two groups also, i.e., the 24 patients in Group 1 who received mecamylamine alone and the 80

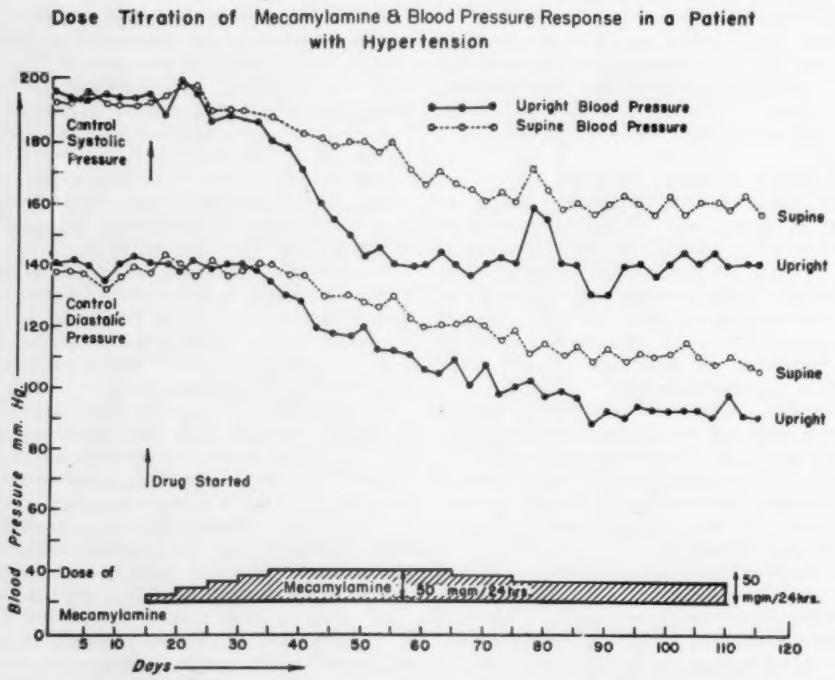


Fig. 1.—Typical dose response to mecamylamine. As the dose is progressively increased, the blood pressure decreases as the optimal dose is reached. The blood pressure response is primarily in the upright position.

TABLE 3.—*Comparison of the Blood Pressure Response to Mecamylamine Used Alone and Mecamylamine Combined with Rauwolfia*

	Group 1 (Mecamylamine Alone)				Group 2 (Mecamylamine + rauwolfia)			
	Supine		Upright		Supine		Upright	
	No.	%	No.	%	No.§	%	No.	%
Subgroup A (control upright diastolic blood pressure > 100 mm. Hg but < 120 mm. Hg)								
Number of patients treated	10	100	10	100	15	100	15	100
Responsive*	1	10	6	60	7	47	12	80
Unresponsive	9	90	4	40	8	53	3	20
Normotensive†	0	0	4	40	2	13	5	33
Average dose‡ of responders			23 mg.				18 mg.	
Average dose‡ of nonresponders			28 mg.				16 mg.	
Subgroup B (control upright diastolic blood pressure >120 mm. Hg)								
Number of patients treated	14	100	14	100	64	100	65	100
Responsive*	7	50	10	71	38	59	63	97
Unresponsive	7	50	4	29	26	41	2	3
Normotensive†	1	7	4	29	3	5	25	38
Average dose‡ of responders			34 mg.				27 mg.	
Average dose‡ of nonresponders			36 mg.				25 mg.	
Totals (subgroups A & B)								
Number of patients treated	24	100	24	100	79	100	80	100
Responsive*	8	33	16	67	45	57	75	94
Normotensive†	1	4	8	33	5	6	30	38
Average dose‡ of responders			29 mg.				23 mg.	

* Reduction in mean blood pressure (diastolic plus one-third of pulse pressure) of 20 mm. Hg or more.
† Blood pressure reduced to below 150/100.
‡ This refers to the dose of mecamylamine given over a 24-hour period.
§ We were unable to make observations in one patient in the supine position owing to severe deformity of the spine.

patients in Group 2 who received mecamylamine and rauwolfia together. Each of the main treatment groups have been subdivided into two subgroups (A and B) on the basis of degree of elevation of their diastolic blood pressure prior to therapy. Subgroup A consists of patients with less severe disease whose control diastolic upright blood pressure was more than 100 but less than 120 mm. Hg, whereas in Subgroup B the control upright diastolic pressure was more than 120 mm. Hg.

The results obtained with mecamylamine alone (Group 1) and combined with rauwolfia (Group 2) are summarized in Table 3. Of the patients with less severe disease (Subgroup 1A) who received mecamylamine alone for four months or more, 60% were responsive, i. e., obtained a reduction in mean blood pressure (diastolic plus one-third the pulse pressure) of 20 mm. Hg or more, in the upright position, but only 10% were responsive when they remained supine. Forty per cent were normotensive (blood pressure reduced to 150/100 or less) in the upright position, whereas none became normotensive while remaining supine. A comparable number of patients with more severe disease (Subgroup 1B) responded to mecamylamine, 71% obtaining a significant reduction in the upright blood pressure and 29% becoming normotensive.

The patients in Group 2, who received mecamylamine and rauwolfia in combination, responded more satisfactorily as a group when compared with the patients who received mecamylamine alone (Group 1).

TABLE 4.—*Comparison of the Blood Pressure Response to Mecamylamine plus Rauwolfia During Two Consecutive Three-Month Periods (D_1 and D_2) in the Same Patients*

	Period D_1				Period D_2			
	Supine		Upright		Supine		Upright	
	No.	%	No.	%	No.	%	No.	%
Subgroup A (control upright diastolic blood pressure > 100 mm. Hg but < 120 mm. Hg)								
Number of patients treated	6	100	6	100	6	100	6	100
Responsive*	3	50	4	67	2	33	5	83
Unresponsive	3	50	2	33	4	67	1	17
Normotensive†	1	17	1	17	0	0	4	67
Average dose of responders	15 mg.				28 mg.			
Subgroup B (control upright diastolic blood pressure > 120 mm. Hg)								
Number of patients treated	28	100	29	100	28	100	29	100
Responsive*	13	46	25	86	18	64	28	97
Unresponsive	15	54	4	14	10	36	1	3
Normotensive†	0	0	9	31	0	0	16	55
Average dose of responders	22 mg.				30 mg.			
Totals (Subgroups A & B)								
Number of patients treated	34	100	35	100	34	100	35	100
Responsive*	16	47	29	83	20	59	33	94
Normotensive†	1	3	10	29	0	0	20	57

†* See footnote to Table 3.

TABLE 5.—*Side-Effects of Mecamylamine Alone Compared with Effects of Mecamylamine with Rauwolfia*

Side-Effects	Mecamylamine Alone		Mecamylamine + Rauwolfia	
	Patients with Complaint, No.	% of Total*	Patients with Complaint, No.	% of Total*
Total patients, No.	24	100	80	100
Anorexia	7	29	4	5
Increased appetite	2	8	18	23
Nausea	8	33	9	11
Vomiting	3	13	2	3
Constipation	19	79	55	69
Moderate	14	58	46	58
Marked	5	21	9	11
Nasal congestion	9	38	26	33
Angina	2	8	3	4
Weakness	16	67	37	46
Moderate	13	54	33	41
Marked	3	13	4	5
Palpitations	3	13	5	6
Blurred vision	13	54	34	43
Sedation	9	38	45	56
Dizziness	11	46	36	45
Syncope	1	4	4	5
Dry mouth	16	67	33	41
Sense of well-being	8	33	14	18
Impotence†	4	50	18	60
Bladder atony	1	4	4	5

* Per cent of patients treated.
† Only those patients are included in whom this side-effect was critically evaluated.

Of the patients with less severe disease (Subgroup 2A), 80% became responsive and 33% became normotensive in the upright position as compared with 47% and 13%, respectively, in the supine position. Of the patients in Subgroup 2B, with more severe disease, 97% responded and 38% became normotensive in the upright position and 59% and 5%, respectively, in the supine position. Therefore, severity of disease did not alter the responsiveness of these patients, since the response rate was slightly better in the patients with severer disease, an attribute of ganglionic blocking agents in general.

In Table 4 are presented two successive treatment periods for 35 of the 80 patients who received rauwolfia plus mecamylamine. Period D_1 is the first three-month period following the establishment of an effective dose of mecamylamine, and Period D_2 is the second three-month (or longer) period. It is obvious that with extended therapy more effective reduction in blood pressure was obtained. For example, during Period D_2 the over-all response rate was 94%, as compared with 83% during the first treatment period (D_1), and the normotensive rate was increased from 29% during Period D_1 to 57% during Period D_2. This was no doubt due to the establishment of a more individualized and effective dosage schedule for each patient.

In Table 5 a comparison of the side-effects of mecamylamine alone (Group 1) and mecamylamine combined with rauwolfia (Group 2) is presented. The major side-effects of mecamylamine alone and mecamylamine plus rauwolfia are qualitatively similar, although there are quantitative differences. Twenty-nine per cent of the patients receiving mecamylamine alone complained of anorexia, whereas only five per cent receiving combined therapy lost their appetite. In fact, 23% of the patients receiving mecamylamine and rauwolfia experienced increased appetite. This increase in appetite was probably due to the rauwolfia. Nausea was noted in a higher incidence (33%) of those patients receiving mecamylamine alone, but vomiting was present in only three. The incidence of constipation was slightly higher (79% as compared with 69%) in the patients receiving mecamylamine alone, as was the severity of the constipation. The lower incidence of this side-effect in the patients receiving mecamylamine and rauwolfia (Group 2) was probably due to the intestinal stimulant effect of the rauwolfia. Nasal congestion was present in about one-third of the patients receiving mecamylamine alone and was essentially the same in the patients receiving mecamylamine plus rauwolfia, but the severity was much more marked in the latter group. Only 4% to 8% of the patients in either group experienced angina. Weakness was present in two-thirds of the patients receiving mecamylamine alone, which was somewhat greater than in those patients receiving mecamylamine plus rauwolfia (46% in the latter patients). Palpitations were present in three (13%) of the patients receiving mecamylamine alone and in five (6%) of the patients receiving mecamylamine plus rauwolfia. Blurred vision was also slightly commoner in those patients receiving mecamyla-

TABLE 6.—*Comparison of the Side-Effects of Therapy with Mecamylamine and Rauwolfia During Two Consecutive Periods in the Same Thirty-Five Patients**

	Mecamylamine + Rauwolfia			
	Period D_1		Period D_2	
	Patients with Complaint, No.	% of Total	Patients with Complaint, No.	% of Total
Total patients, No.	35	100	35	100
Anorexia	2	6	4	11
Increased appetite	5	14	5	14
Nausea	6	17	6	17
Vomiting	1	3	2	6
Constipation	19	54	23	66
Moderate	18	51	21	60
Marked	1	3	2	6
Nasal congestion	15	43	13	37
Angina	2	6	2	6
Weakness	19	54	18	51
Moderate	16	46	16	46
Marked	3	9	2	6
Palpitations	3	9	2	6
Blurred vision	10	29	16	46
Sedation	17	49	25	71
Dizziness	17	49	20	57
Syncope	0	0	3	9
Dry mouth	11	31	12	34
Sense of well-being	3	9	4	11
Impotence*	4	67	6	75

* See footnotes to Table 5.

mine alone (54% as compared with 43%). Sedation occurred in 38% of the patients receiving mecamylamine alone and in 56% of the patients receiving mecamylamine plus rauwolfia. Dry mouth was present in both groups of patients but was more severe in the patients receiving mecamylamine alone. Impotence was observed in about one-half of the patients in both groups.

In order to evaluate the effect of continued treatment, the incidence of side-effects during two consecutive three-month periods (Periods D_1 and D_2) in the 35 patients treated for six months or more has been presented in Table 6. It is obvious that there is very little difference in the incidence of the side-effects, but the side-effects were better controlled with more prolonged therapy in many instances. For example, the patients learned to control constipation with judicious use of cathartics so that this was less frequently a problem after six months of therapy. If untreated, this was the most serious and annoying problem encountered. Neostigmine (Prostigmin) bromide in doses of 15 to 30 mg. or pilocarpine in doses of 5 to 10 mg. given 30 minutes before each meal was tried. If this was inadequate, cathartics were tride, 3 drams (12 cc.) of tincture of cascara sagrada, or ½ oz. (15 cc.) of magnesia magma, or both. If ileus threatened, magnesium sulfate and neostigmine were used and mecamylamine was temporarily stopped. Neostigmine and pilocarpine were more effective in some patients than cathartics, whereas in others cathartics were superior. For some patients irritant cathartics (cascara sagrada and phenolphthalein) were superior, whereas for others magnesium sulfate and magnesia magma (milk of magnesia) were more effective. Therefore, the only way to determine the best antidote for the constipation due to the mecamylamine was by trial and error. In our opinion, the best treatment of the constipation is that regimen which is found by trial and error to be the most effective for each individual patient.

The nasal congestion decreased in intensity in most instances. In those patients with mild nasal congestion initially, this was frequently completely relieved with continued therapy. However, in some instances the intensity of nasal congestion was such that it became necessary to stop the use of rauwolfia after prolonged treatment. In all such instances the nasal congestion decreased when the rauwolfia was stopped. In milder cases antihistaminics such as tripelennamine (Pyribenzamine), chlorpheninamine (Chlor-Trimeton) maleate U. S.P., or pyrrobutamine (Pyronil) offered moderate relief. If nasal congestion was severe, nasal decongestants such as phenylephrine (Neo-Synephrine) or tetrahydrozoline (Tyzine) became necessary.

Weakness, which was frequently noted, was seen during periods in which the blood pressure decreased excessively. This was also an intermittent complaint and could be corrected well with the degree of blood pressure reduction. In only two instances was this severe enough after six months that discontinuing therapy with mecamylamine was contemplated.

The incidence of blurred vision was

TABLE 7.—*Symptoms Improved with Therapy*

	Per Cent of those Patients with Symptom Prior to Treatment					
	Mecamylamine Alone			Mecamylamine + Rauwolfia		
Symptoms improved	Group A	Group B	Total	Group A	Group B	Total
Bradycrotic response	0	21	13	50	50	50
Headache	30	71	54	89	67	71
Angina	50	75	67	0	77	75
Congestive heart failure	50	75	63	100	78	81
Renal impairment	0	20	13	20	25	25
Cardiac enlargement (x-ray)	0	20	14	20	34	31
Abnormal electrocardiogram	0	29	13	22	27	26
Funduscopic (Grades 3 & 4)	----	*	*	33	64	59

* Complete data not available.

higher after three months of therapy (46%) than it was during the initial period (29%). This was probably due to the larger doses of mecamylamine being used during Period D_2. However, the increase in incidence may have been due in part to the patients becoming more aware of this complaint as time went on. During the interrogation of the patient, attempts were made not to suggest symptoms which would be considered side-effects to the drug. Therefore, it frequently took a period of time before the patient became conscious of some of the minor symptoms.

Sedation was a rather prominent symptom, which also increased in frequency but not in intensity during Period D_2. It was noted that when mecamylamine was added to the rauwolfia, sedation was more marked than it was when rauwolfia was used alone. This would be anticipated, since, some of the patients were sedated who received mecamylamine alone, apparently owing to the central effect of this drug. The sedative properties of rauwolfia are well established.

Dry mouth was frequently rather severe, and a few of the patients complained of loss of appetite and inability to taste be-

TABLE 8.—*Symptoms Improved with Therapy (Mecamylamine plus Rauwolfia) During Two Successive Treatment Periods*

	Per Cent of Patients with Symptom Prior to Treatment					
	Period D_1			Period D_2		
Symptom Improved	Group A	Group B	Total	Group A	Group B	Total
Bradycrotic response	83	55	60	67	48	51
Headache	67	53	55	100	71	75
Angina	0	60	60	0	60	60
Congestive heart failure	0	73	73	0	73	73

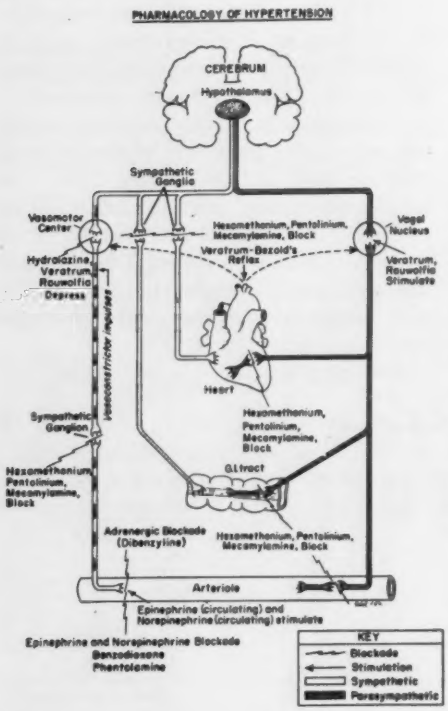


Fig. 2.—Diagramatic representation of the pharmacodynamics of blockade of vasoconstrictor impulses in the autonomic nervous system. As the vasoconstrictor impulses travel over the sympathetic nervous system, they can be blocked in the brain (central blockade), at the sympathetic ganglia (ganglionic blockade), or peripherally at the blood vessels (adrenergic blockade). There is very little difference between the ganglionic blockade of the sympathetic nervous system in comparison with that of the parasympathetic nervous system. Therefore, when the blood pressure is reduced with the use of a ganglionic blocking agent side-effects due to parasympathetic ganglionic blockade are nearly always observed.

cause of the lack of salivation. If severe, it became difficult to swallow food, and glossitis was observed in two patients. However, this improved despite continued therapy. Pilocarpine in a dose of 5 to 10 mg. given 30 minutes before meals was the most effective antidote for the depression of salivation.

Definite conclusions as to relief of symptoms by therapy in the current study cannot be drawn because of the relatively short period of follow-up. However, definite trends were observed (Tables 7 and 8). There was a high incidence of symptoms and complications associated with the hypertensive vascular disease in these patients. The combination of mecamylamine and rauwolfia seemed to be superior to mecamylamine alone as far as improvement in symptomatology was concerned. The outstanding symptomatic improvement noted in this group was the relief of headache and improvement of heart failure without any alterations in the therapeutic program other than the institution of the antihypertensive regimen. Ten of thirteen patients with angina showed definite improvement.

Half of the patients showed a reduction in pulse rate of 10 beats or more in both the supine and the upright position after receiving mecamylamine and rauwolfia for four months or more.

One-fourth of the patients demonstrated electrocardiographic evidence of improvement, and in 31% the heart size decreased as observed by roentgenological examination. One-fourth of the patients with evidence of renal damage showed improvement. This was particularly noteworthy in the patients who had red cells in their urine on microscopic examination prior to treatment.

In the comparison of symptomatic improvement in the 35 patients in Group 2 who were studied for six months or more on whom the results were analyzed for two successive drug periods (D_1 and D_2), there was very little difference between periods. Apparently the initial reduction in blood pressure had the most dramatic effect on the symptoms due to hypertensive vascular disease.

Comment and General Considerations

Pharmacology.—Mecamylamine is a ganglionic blocking agent which apparently blocks both the sympathetic and parasympathetic ganglia. Therefore, when doses adequate to block the sympathetic ganglia, and consequently lower the blood pressure, are administered, one can expect to also observe the effects of parasympathetic blockade. Under these circumstances responses due to parasympathetic blockade are considered side-effects, since only blockade of the sympathetic ganglia is desired. Pharmacologically speaking, however, the symptoms produced by parasympathetic blockade are to be expected and are the normal response to ganglionic blocking agents. Therefore, it is not surprising that dry mouth and decreased intestinal peristalsis are rather prominent symptoms associated with the administration of ganglionic blocking agents such as mecamylamine, pentolinium, and hexamethonium. A diagrammatic representation of the drugs which are effective in lowering the blood pressure in patients with hypertension is presented in Figure 2. Here one can visualize the rationale for administering a ganglionic blocking agent along with a centrally acting agent such as rauwolfia or hydralazine, since both depress the sympathetic nervous system but in different anatomical areas. In the current study, mecamylamine and rauwolfia were administered to 80 patients. When this is done, the rauwolfia depresses the sympathetic nervous system (vasopressor impulses) in the brain whereas the administration of mecamylamine further blocks the outflow of vasoconstrictor impulses as they travel over the sympathetic nervous system through the ganglia. This combination allows for a more effective lowering of the blood pressure, with less variability from time to time.

The duration of action of mecamylamine

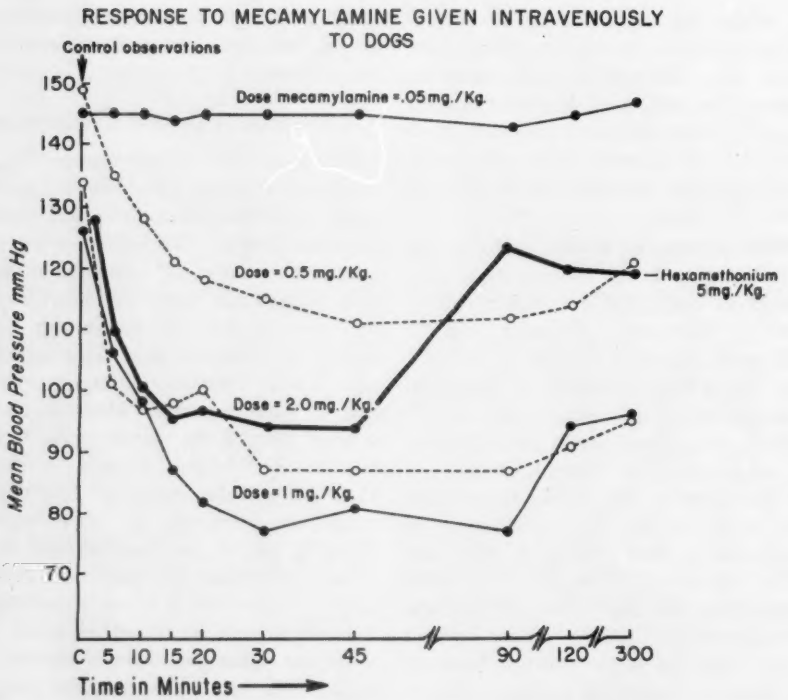


Fig. 3.—Blood pressure response to increasing doses of mecamylamine given intravenously to four groups of four dogs each anesthetized with 30 mg/kg. of pentobarbital. The maximum effect was observed in a dose of 1 mg/kg.; giving a larger dose had no additional effect on blood pressure. The degree of blood pressure reduction roughly compared with hexamethonium but was much more prolonged. (Adapted with permission from Ford, Madison, and Moyer,[6] *The American Journal of Medical Sciences,* Philadelphia, Lea & Febiger.)

is much longer than that of hexamethonium. For example, in Figure 3 the blood pressure response to hexamethonium given intravenously to dogs is compared with that obtained with increasing doses of mecamylamine given by the same route. The maximum reduction in blood pressure was reached at 1 mg/kg. of mecamylamine, and giving an additional dose of 2 mg/kg. apparently had no additional hypotensive effect. A dose of 5 mg/kg. of hexamethonium was equally hypotensive. However, 40 minutes after the administration of hexamethonium the blood pressure gradually increased, and after 80 minutes it had returned to the control level, whereas 5 hours after the administration of mecamylamine the blood pressure remained moderately depressed.

TABLE 9.—*Comparison Of Blood Pressure Response To Mecamylamine Administered Orally and Parenterally in Eleven Patients*

	Route of Mecamylamine Administration	
	Intramuscular	Oral
Control blood pressure		
Supine	203/125	203/126
Upright	181/120	186/119
Lowest blood pressure after mecamylamine		
Supine	160/97	165/98
Upright	118/82	122/81
Mean upright blood pressure		
Control	138	141
After mecamylamine	94	95
Duration* (hours)	21	22
Onset of action* (minutes)	46	37

* Mean blood pressure reduced more than 20 mm. Hg.

The outstanding attribute of mecamylamine is that it is equally as effective when given orally as when given parenterally. These observations are summarized in Table

9. It is obvious that in equal doses the effect on the blood pressure is almost identical by the two routes of administration. In addition, the length of action is about the same and the incidence of side-effects about the same. However, in some patients there was more of a delay before the blood pressure decreased after oral administration as compared with the parenteral route and vice versa.

Observations have been made on the effect of blood pressure reduction with mecamylamine on renal hemodynamics in eight patients.[6] After suitable control observations on glomerular filtration rate as determined by inulin clearance and renal plasma flow as determined by *p*-aminohippurate clearance,[5] mecamylamine was administered for two months or more. An attempt was made to adjust the dose of mecamylamine so that an optimal reduction in blood pressure was obtained, i. e., so that the blood pressure in the upright position would be approximately 150/100. Although the reduction in blood pressure was usually associated with a slight reduction in glomerular filtration rate, this was not statistically significant ($P > 0.05$) for the group of eight patients who were treated for two months or more. For example, the average glomerular filtration rate prior to therapy was 80 cc. per minute, whereas after blood pressure regulation it was 68 cc. per minute ($P > 0.20$) in the supine position. Renal plasma flow followed a similar course in that prior to therapy in the supine position it was 506 cc. per minute and after blood pressure reduction for two months or more it was 451 cc. per minute. A typical response of a patient in the supine position is seen in Figure 4A. In this patient the mean blood pressure was reduced from 160 to 128 mm. Hg. This was associated with a reduction in glomerular filtration rate from 86 to 81 cc. per minute and in renal plasma flow from 465 to 409 cc. per minute.

Although renal hemodynamics were not depressed markedly with moderate reduction in blood pressure, when the blood pressure

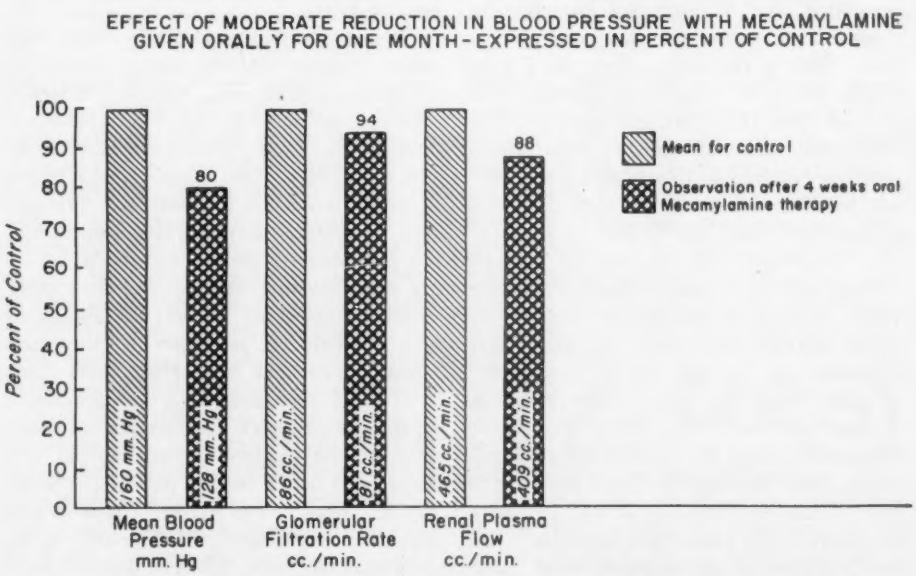


Fig. 4A.—Renal hemodynamic response to chronic administration of mecamylamine given orally for one month. Observations were made in the supine position. There was a slight reduction in renal plasma flow and glomerular filtration rate associated with moderate reduction in mean blood pressure. However, this did not impair renal function significantly.

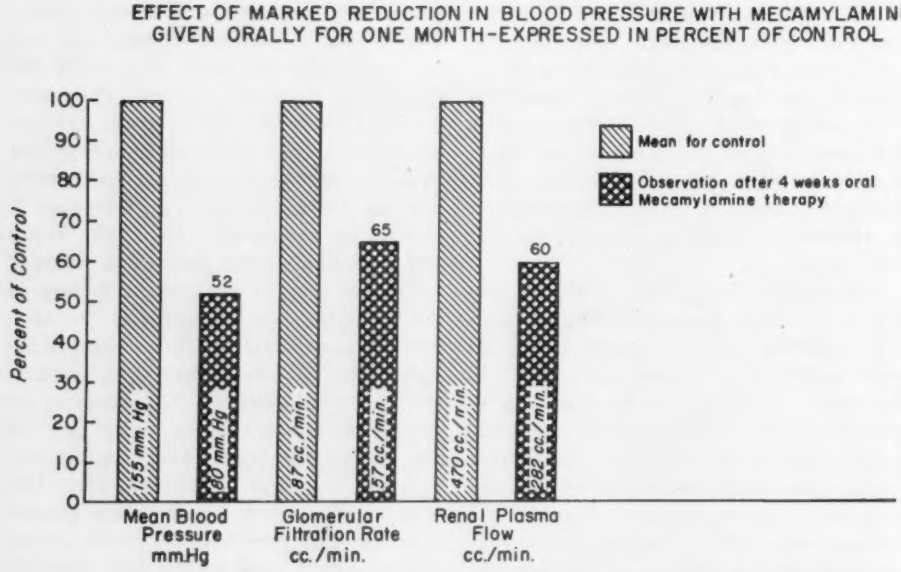


Fig. 4B.—In this patient an excessive reduction in blood pressure was produced by the administration of mecamylamine. When this occurred, there was a relatively marked reduction in glomerular filtration rate and renal plasma flow even in the supine position. This is of significance in the patient who has impaired renal function, since reduction in glomerular filtration rate of this degree would decompensate the kidney further.

was reduced excessively this was frequently associated with a significant reduction in glomerular filtration rate and renal plasma flow. Such a response is seen in Figure 4B, in which the mean blood pressure was reduced from 155 to 80 mm. Hg (100/70). When this occurred, the glomerular filtration rate was reduced from 87 cc. per minute to 57 cc. per minute and the renal plasma flow from 470 to 282 cc. per minute. Although this is not of serious consequence in the patient who has adequate renal function, in the patient with severe renal damage depression of glomerular filtration rate to this degree can readily produce renal functional decompensation. Should this occur, it is readily reversed by merely decreasing the dose of the mecamylamine, thus allowing the blood pressure to rise to mild hypertensive levels. Probably, in practice, the blood urea introgen is the best estimate of compensated renal function. As long as the blood urea nitrogen is within normal limits one can conclude that serious depression in glomerular filtration rate and associated renal functions has not occurred.

Despite ganglionic blockade, when the patient changes from the supine position to the upright position renal vascular resistance increases, owing to the fact that renal blood flow decreases more than mean blood pressure (Fig. 4C). This is associated with an equivalent reduction in glomerular filtration rate. Therefore, the orthostatic reduction in blood pressure in the patient who is receiving mecamylamine therapy (as with other ganglionic blocking agents) is associated with a significant reduction in glomerular filtration rate and renal blood flow. This is of some importance to note, particularly in the patient who has received an overdose of the blocking agent. Should this occur, it is better for the patient to remain supine, since under these circumstances maximum renal function is obtained during ganglionic blockade. When he is ambulatory, further reduction in renal function occurs and, consequently, further aggravation of the renal failure, which may have been only

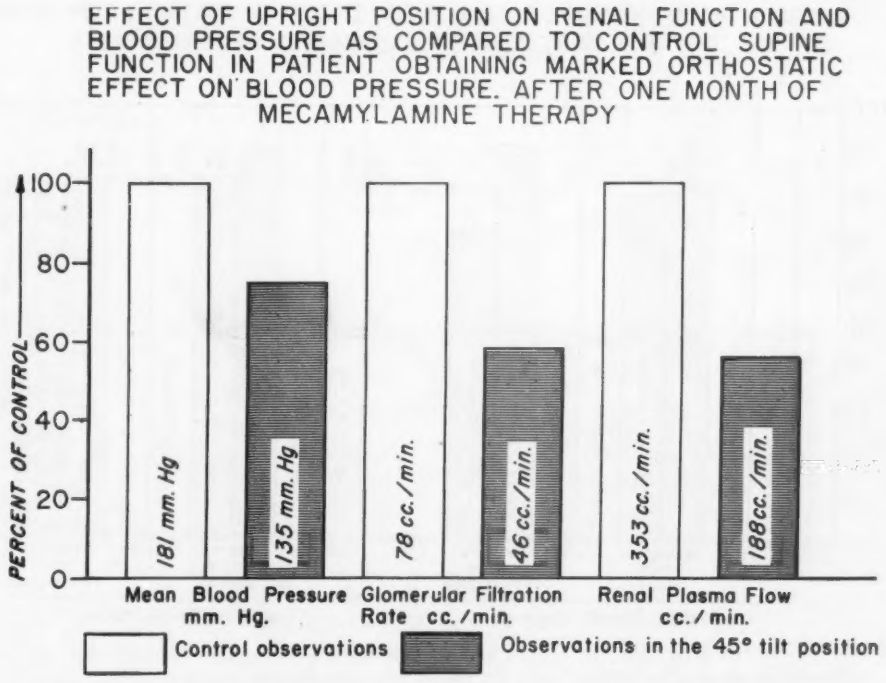


Fig. 4C.—Effect of the upright position as compared to the supine in a patient who is blocked with mecamylamine. As the blood pressure decreases there is a sharp reduction in glomerular filtration rate and renal plasma flow, due apparently to renal vasoconstriction, as a reflex to the standing position.

border-line in the supine position. Increase in glomerular filtration rate in the supine position is also reflected in an increase in urine volume and sodium excretion immedlately after these patients go to bed at night. This transient increase in urinary volume immediately after assumption of the supine position in patients who have previously been ambulatory for a prolonged period is a common response seen in patients being treated with any of the currently available ganglionic blocking agents.

In order to test the orthostatic effect of mecamylamine alone as compared with mecamylamine plus rauwolfia, observations were made on a group of patients who received mecamylamine as the sole therapeutic agent following which reserpine was added in a dose of 1 mg. per day. This was done to see if the rauwolfia (reserpine) would decrease the orthostatic effect on the blood pressure. The results in this study are summarized in Figure 5. It is obvious that the orthostatic effect was not reduced, so that blood pressure decreased just as much when the patient stood up (orthostatic effect) when they received mecamylamine plus reserpine as it did when they received mecamylamine alone. This was true for both the systolic and diastolic blood pressures. However, after reserpine was added a greater reduction in blood pressure occurred for the same dose of mecamylamine. For example, the upright systolic blood pressure decreased from an average value of 80% of the control to 72% of the control after the reserpine was added and from 84% to 75% diastolic after the administration of reserpine, which proved to be statistically significant ($P<0.05$). This therefore indicates that an additional hypotensive effect was obtained from the reserpine but that

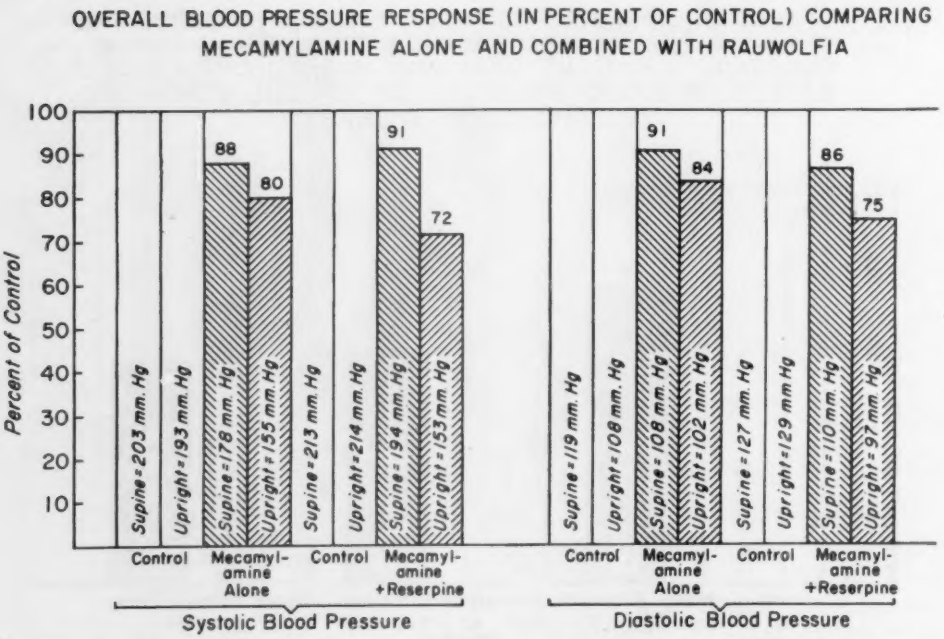


Fig. 5.—Over-all values in systolic and diastolic blood pressure after administration of mecamylamine alone as compared with the response to mecamylamine plus rauwolfia.

the orthostatic effect of the mecamylamine was not decreased by adding reserpine to this agent.

Clinical Considerations.—Although mecamylamine appears to be an effective drug for reducing the blood pressure in patients with severe hypertension, certain problems arise in the management of these patients. It is particularly difficult to adjust the dose exactly so that the blood pressure remains stable throughout a 24-hour period. Individualization of the dose regimen of each patient is extremely important. We have observed patients who obtained an adequate response on a dose of mecamylamine of 2.5 mg. given twice a day. Contrariwise, some of our patients have required as much as 160 mg. per day. The use of an average dose is impossible and will surely lead to an intolerable incidence of complications. Figure 6 demonstrates the response of two different patients to the same dose of mecamylamine. Patient 1 obtained no reduction in blood pressure when given 10 mg. of mecamylamine parenterally. Patient 2 obtained no reduction in blood pressure when given a placebo injection, but when he was given 10 mg. of mecamylamine there was an excessive reduction in blood pressure associated with moderately severe side-reactions. This example demonstrates the point that a dose of the blocking agent which is applicable to one patient may not be applicable to another. Generally speaking, the more severe the hypertensive vascular disease, the greater the dose requirement of mecamylamine.

Another problem in dose adjustment is prolonged length of action of mecamylamine and the development of partial tolerance after the first one to three weeks. Therefore it becomes necessary to adjust the dose very slowly over this period of time. Owing to the prolonged action of mecamylamine, after it is started there is progressively increasing effect of the drug for the first three days, following which the blood pressure response stabilizes. Then, after a

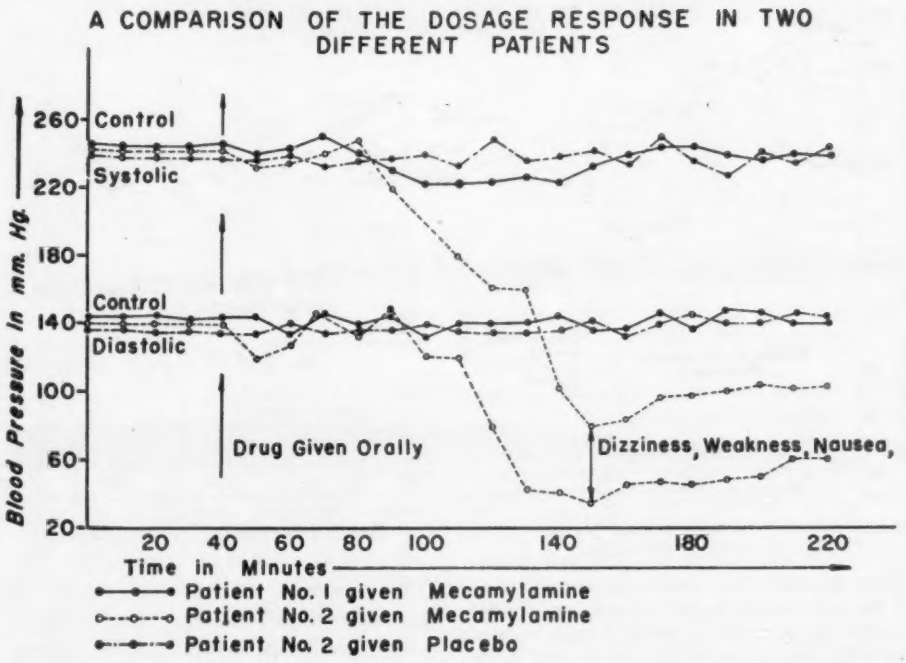


Fig. 6.—A comparison of two patients who obtained different degrees of response from the same dose of mecamylamine. See text for description.

variable period of one to three weeks, partial tolerance develops so that it is necessary to increase the dose of the drug (usually from 10% to 50%) in order to maintain an adequate reduction in blood pressure. After the second titration procedure, the dose usually remains constant and it is rarely again necessary to increase the daily intake. A more or less typical patient is illustrated in Figure 7, Case 1. This patient was started on rauwolfia, receiving rauwolfia alone for over seven weeks, with little reduction in blood pressure. When 5 mg. of mecamylamine was then given twice a day there was a marked reduction in blood pressure initially, but as the drug was continued at the same dose for another two weeks there was less reduction in blood pressure, so that it became necessary to progressively increase the dose up to 30 mg. a day (5 mg.-15 mg.-10 mg). After this dose had been continued for six weeks, the side-reactions decreased and it was possible to increase the dose another 10 mg. per day. On this dose, the patient's blood pressure was well regulated.

CASE 1.—A 42-year-old white physician (Fig. 7) was first seen complaining of severe backaches frequently associated with nausea and vomiting in the morning. On several occasions he had had rather marked exertional and nocturnal dyspnea, for which he had been digitalized. On three occasions during the previous two months he had noticed peripheral edema which lasted for several days at a time. Physical examination revealed a well-developed white man in no acute distress. On funduscopic examination small punctate retinal hemorrhages were found throughout both eyes but papilledema was not present. On examination of the cardiovascular system, the blood pressure was 210/130 in the supine position and 190/145 in the upright position. The heart was enlarged to the left, and he had a Grade 1 apical systolic murmur. There was no peripheral edema and no hepatic enlargement. The lungs were clear to auscultation and percussion. On laboratory examination, the specific gravity of the urine was 1.022; there was 1+ albuminuria, and an occasional red cell was seen in the urine. A diagnosis of severe essential hypertension in the premalignant phase was made.

The patient was started on placebo, which he received for three weeks without effect on the

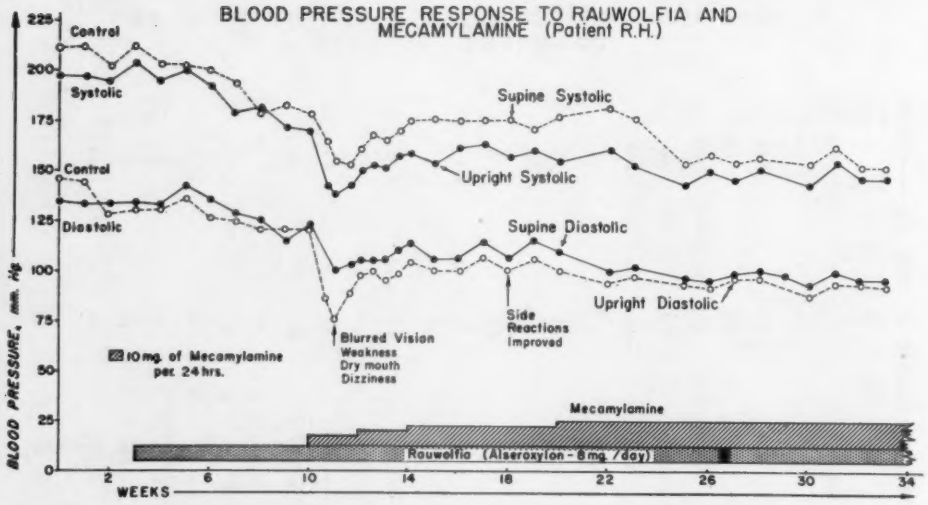


Fig. 7 (Case 1).—Blood pressure response to combined alseroxylon and mecamylamine therapy. See text for description.

blood pressure. Then alseroxylon was started in a dose of 2 mg. given four times a day. On this medication there was a slight reduction in blood pressure both in the upright position and in the supine position (Fig. 7). It was thought, because of the severity of the disease, that this patient would require adjunctive therapy in the form of a ganglionic blocking agent. Therefore, mecamylamine was started in a dose of 5 mg. twice a day. This dose caused a sharp reduction in blood pressure, to 140/75 in the upright position and 150/105 in the supine position. In association with the reduction in blood pressure, the patient complained of blurred vision, weakness, dry mouth, and dizziness when standing. Despite continued medication, this marked response was gradually lost over the the next two weeks, and so it became necessary to increase the dose another 10 mg. in order to maintain the blood pressure at approximately 150/100 in the upright position. Two weeks later it became necessary to increase the dose another 10 mg., and six weeks later it was increased another 10 mg. On this dosage schedule the patient's blood pressure was very well regulated and has remained so for at least two months. As therapy has continued, there has been some reduction in the orthostatic effects, so that the blood pressure is only slightly lower when the patient stands as compared with supine position.

This patient demonstrates the necessity for careful adjustment of the dose; after an adequate initial response it frequently becomes necessary to increase the dose (owing to development of partial tolerance) if this response is to be maintained. As therapy continued and the blood pressure remained well regulated, the patient's symptoms completely disappeared; headaches were relieved, the retinal hemorrhages cleared up, and he did not complain of exertional or nocturnal dyspnea. After three months there was marked reduction in heart size.

Some patients showed a very marked reduction in blood pressure in the upright position, with considerably less response in the supine position. We have found no way to effectively overcome this problem. None the less, these patients seemed to obtain marked relief of their symptoms with intermittent reduction in blood pressure (while the patients were up and about). Such a case is seen in Case 2, Figure 8.

CASE 2.—A 60-year-old white railroader had had moderately severe hypertension for seven years. For this reason he had been on a low-sodium rice diet. He had had a sympathectomy and had also received hydralazine (Apresoline), veratrum, and numerous other antihypertensive agents, without effect. One year previously he had had a cerebrovascular accident, from which he had recovered. On physical examination he had 3+ eyegrounds (Keith - Wagener - Barker Classification), with marked retinal hemorrhages. Papilledema was not present. The heart was markedly enlarged to the

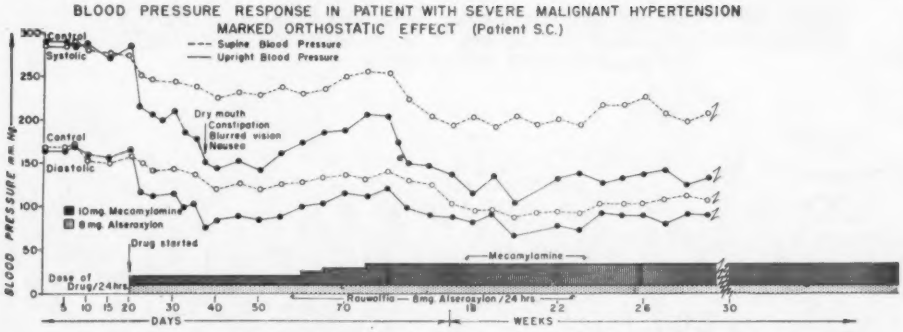


Fig. 8 (Case 2).—Response in patient who obtained excessive orthostatic effect with mecamylamine. See text for description.

left; there was no overt evidence of heart failure.

Laboratory Examination.—The specific gravity of the urine was 1.018. On microscopic examination numerous red cells were found but no white cells. The hemogram was normal. The electrocardiogram showed severe myocardial damage.

During the initial work-up and for a two-week period thereafter, the patient was given a placebo, without effect on his blood pressure. Because of the severity of his disease, the patient was started on 8 mg. of alseroxylon (Rauwiloid) and 10 mg. of mecamylamine (5 mg. twice a day) concurrently. With this therapy he promptly obtained a reduction in the upright blood pressure ranging between 150 to 170 systolic and 70 to 90 diastolic.

Despite the marked orthostatic effect on the blood pressure after therapy was instituted, there were no symptoms associated with the sharp reduction in blood pressure when changing from the supine to the upright position, indicating a very rapid cerebral vascular adjustment to these changes. The patient's therapy has continued unchanged, and his symptoms have improved. His retinal hemorrhages have cleared up, and the side reactions initially exhibited to the drug have decreased. The only problem that he now has is that of occasional constipation, which is handled quite adequately with 10 cc. of cascara sagrada as needed. His course is summarized in Figure 8.

This patient, then, demonstrates the marked orthostatic effect that is occasionally observed with ganglionic blocking agents, in this case mecamylamine. There is very little that can be done to improve the poor supine response, but, despite this, the patient seemed to do very well with intermittent reduction in his blood pressure, since he is upright for 16 to 18 hours out of each day.

Some patients displayed a marked early morning reactivity due to mecamylamine. In these patients it became necessary to reduce the night-time dose or, in many instances, discontinue it completely. Also, these patients required a relatively small breakfast dose. A good example of this type of response is seen in Figure 9, Case 3. This patient was started on rauwolfia and mecamylamine in a dose of 5 mg. twice a day, without effect on the blood pressure. When the mecamylamine was increased to 5 mg. four times a day there was a sharp reduction in blood pressure, but there were wide swings in the blood pressure throughout the day. The blood pressure in the early morning usually ranged between 110 to 130 systolic, at which time the patient complained of weakness and occasional dizziness, but by evening it had increased to 150 to 170 systolic. Despite continued medication, the blood pressure gradually increased, and it was necessary to increase the dose of mecamylamine. The noon and supper doses were increased, and on this regimen there was less variability in the blood pressure, but the control of the blood pressure remained inadequate. The dose was then increased so that the patient received 5 mg. of mecamylamine at breakfast, 15 mg. at lunch, 15 mg. at supper, and none at bedtime. On this dosage the blood pressure was well regulated throughout the day, in fact, the morning blood pressure was usually a little higher than the blood pressure during the remainder of the day. The blood pressure continues to be well regulated on this dosage schedule of rauwolfia and mecamylamine (Figure 9).

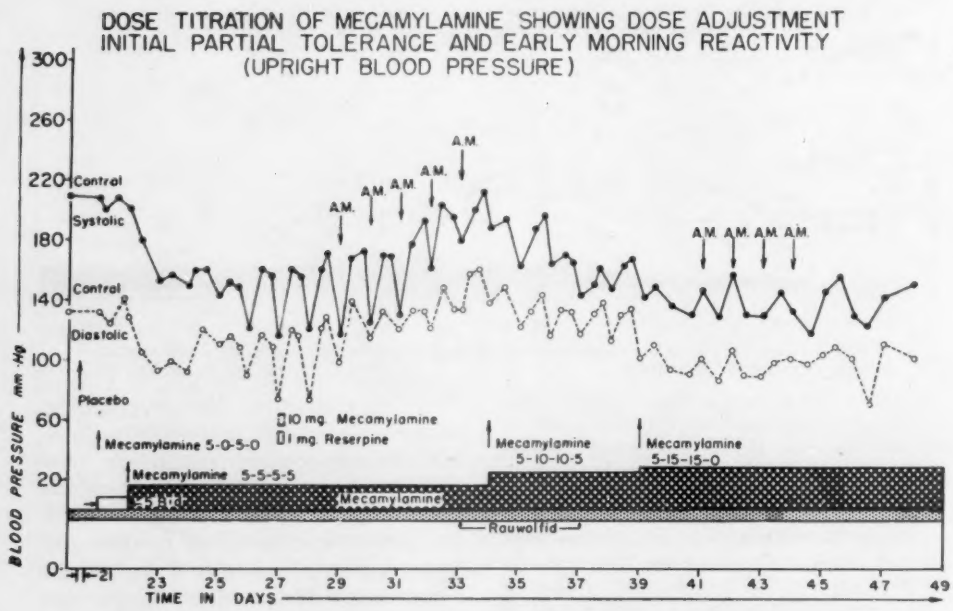


Fig. 9 (Case 3).—Early morning reactivity to the hypotensive effect of mecamylamine, which has been observed in many patients. See text for description.

Case 3.—A 38-year-old white woman was seen for the first time while receiving rauwolfia. Despite the rauwolfia, the blood pressure remained at 190/137. She complained of early morning headaches and occasionally severe precordial pain. Funduscopic examination showed Grade 2+ eyegrounds, with rather marked arteriolar spasm but no hemorrhages or papilledema. The heart was enlarged to the left, and there was an aortic systolic murmur. The chest was clear to auscultation and percussion, and there was no evidence of heart failure. Urinalysis showed occasional red cells with granular casts and 2+ albuminuria. On succeeding urinalyses it was found that the red cells and casts were intermittently present. The specific gravity of the urine was 1.020. The hematological examination was essentially negative. A diagnosis of essential hypertension was made, and the clinical course is summarized in Figure 9.

Despite careful adjustment of dosage over a 24-hour period, it must be remembered that the degree of ganglionic blockade is fixed and does not fluctuate in order to adapt to varying degrees of sympathetic activity. Therefore, if excessive stress is placed on the sympathetic nervous system, more neurogenic impulses will break through the ganglia and, as a result, the blood pressure will increase. This situation is comparable to that of the diabetic patient who receives a fixed dose of insulin with a variable carbohydrate intake. When the carbohydrate intake exceeds that which is well controlled with this fixed dose of insulin, glycosuria occurs. This is very similar to the hypertensive patient whose blood pressure is regulated by controlling the impulses through the ganglia. If excessive stress is placed on the patient, then the dose of the ganglionic blocking agent will be inadequate and the blood pressure will increase. Such a case is seen in Case 4 (Fig. 10), an insurance company executive with moderately severe hypertension.

Case 4.—An insurance company executive was first seen with moderately severe hypertension, complaining primarily of intermittent precordial pain and morning headaches. He responded well to a combination of rauwolfia and mecamylamine, although he had not responded to placebo over a three-week period previously. The patient seemed to be doing well, with very little variation in blood pressure, and then difficulty developed within his company so that he was placed under a great deal of stress for a period of one week. During this

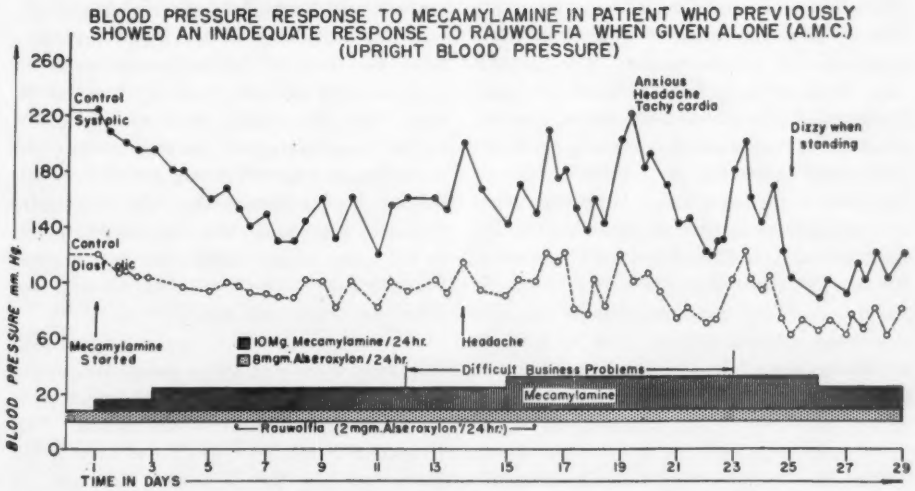


Fig. 10 (Case 4).—The effect of neurogenic stress on the blood pressure in a patient who is receiving ganglionic blockade. See text for description.

period, he had marked spikes in his blood pressure associated with headaches. It was thought best to increase the dose of the mecamylamine, but, despite an increase in dose, on several occasions he continued to have marked spikes in his blood pressure; these were associated with headache, tachycardia, and precordial pain. The patient was subsequently advised to stay away from the office for a period of one week. After the first day at home, his blood pressure dropped to 90/60 and he complained of dizziness when standing. It was then necessary to reduce the dose of mecamylamine, and the blood pressure gradually adjusted to normotensive levels.

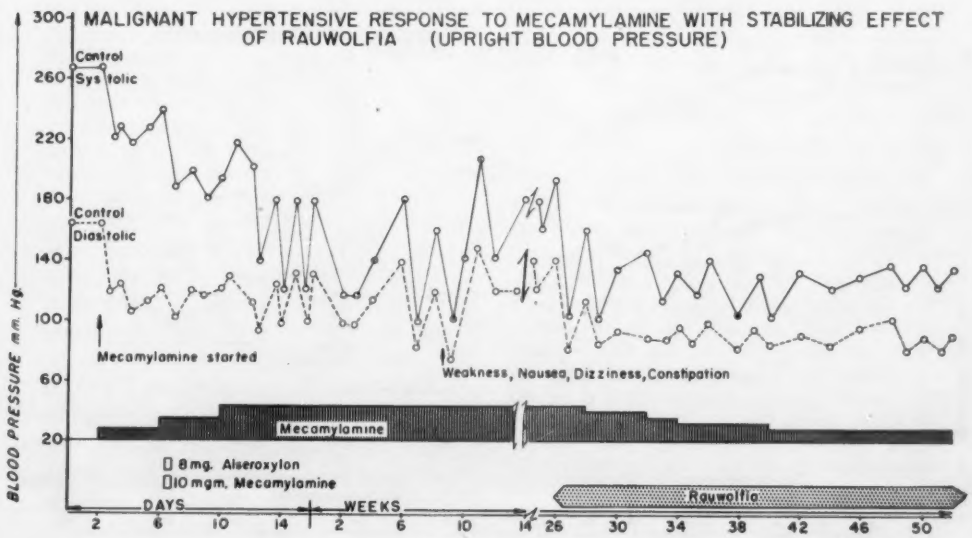


Fig. 11.—The stabilizing effect of rauwolfia on ganglionic blockade. See text for description.

The question can be raised as to the exact role of rauwolfia when it is used in combination with mecamylamine. The over-all data would seem to indicate about the same incidence of side-effects when mecamylamine is used alone as when it is used in combination with rauwolfia, and there is also a comparable response rate. However, when one studies the individual cases over a 24-hour period, it is difficult not to be impressed by the more constant effect and less variability in blood pressure regulation with combined therapy as compared with mecamylamine alone. In addition, the dosage of mecamylamine is frequently less and, as a consequence, there is less blockade of the parasympathetic nervous system, which reduces the severity of the side-effects resulting from blockade of this system, i.e., constipation, dry mouth, and blurred vision.

A typical response is seen in Figure 11. This is a patient who was started on mecamylamine alone and who responded dramatically. However, there was a great deal of variability in the blood pressure, and, in association with the hypotensive swings, weakness, nausea, dizziness, and constipation were frequently rather marked. When rauwolfia was added to the regimen, there was less variability in the blood pressure. Also, the dose of mecamylamine could be progressively reduced from 40 down to 10 mg. a day. As a result, there was less effect on the parasympathetic nervous system and constipation, blurred vision, and dry mouth became less marked. Also, the orthostatic dizziness was noted less frequently, owing to the more stable blood pressure on combined therapy as compared with the response when mecamylamine was used alone.

A side-reaction which is more marked with this drug than with other ganglionic blocking agents, according to our observation, is the degree of dryness of the mouth. This is seen in Case 5 (Fig. 12), a 43-year-old physician. In this instance, the lack of salivation was so marked that it became difficult for him to eat and he developed glossitis which became rather difficult to treat. Because of the severity of his hypertension, it was decided to continue on mecamylamine therapy despite the glossitis. This improved considerably after about two weeks but the patient continues to complain of a severe dry mouth even after a six-month period of follow-up. Talking occasionally

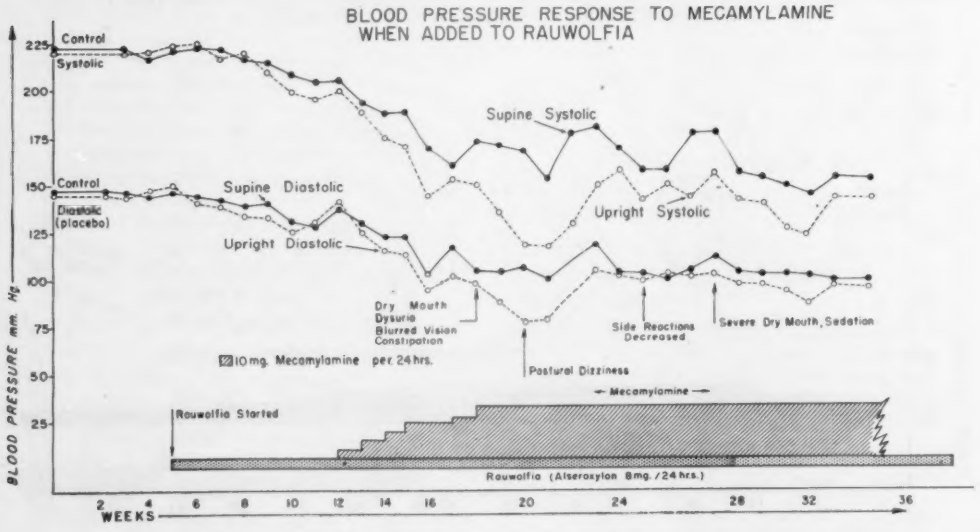


Fig. 12 (Case 5).—Patient who obtained excessive reduction in salivation. Relief was obtained with pilocarpine.

becomes difficult because of the lack of salivation, and eating is a problem, since all of his food has to be washed down with water taken with each bite. Pilocarpine in doses of 5 to 10 mg. given orally 30 minutes before meals seems to be the best antidote for dry mouth and depression of salivation. Neostigmine, 15 to 30 mg. given 30 minutes before meals, was also effective but generally less so than pilocarpine.

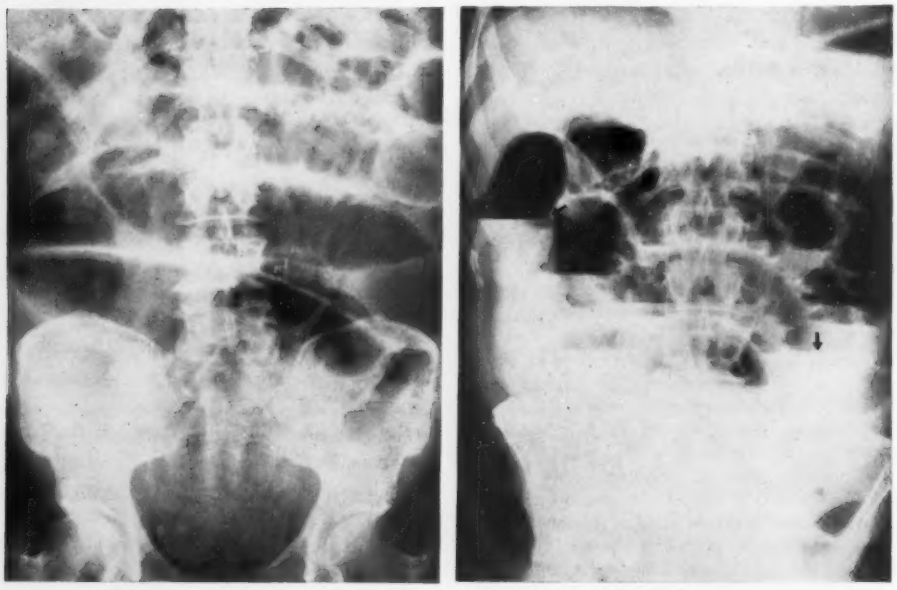
CASE 5.—A 43-year-old physician was in his usual health until four years ago. At that time he was first noted to have hypertension. This was treated by a number of antihypertensive drugs, without effect. One year ago he developed precordial pain and rather severe morning headaches for the first time. These became associated with rather marked anxiety manifestations. One month prior to being seen for the first time by us, he developed complete blindness in one eye due to a retinal hemorrhage. On physical examination the heart was enlarged but there was no evidence of heart failure. On funduscopic examination the patient had retinal hemorrhages bilaterally and slight papilledema. Laboratory examination: There was 1+ albuminuria but no red cells. The specific gravity of the urine was 1.028. An electrocardiogram showed evidence of left ventricular hypertrophy and ischemia. The patient was given a placebo for one month, during which time he underwent psychotherapy by a member of the neuropsychiatric department. During this time he received 25 mg. of chlorpromazine four times a day, which aggravated his anxiety manifestations. He complained bitterly of being unable to concentrate and to sleep at night. The chlorpromazine was then discontinued and rauwolfia was started (alseroxylon, 8 mg. per day). This seemed to have some sedative effect, but it did not reduce his blood pressure significantly. The clinical course from then on is summarized in Figure 12.

Constipation is one of the most constant side-effects of mecamylamine therapy. If this problem is not combated vigorously, it may lead to fecal impactions and subsequently to ileus. Because of the prolonged action and the potency of this drug, the onset of bowel paralysis may be more rapid and the severity of the ileus more marked than with any of the other ganglionic blocking agents which are available for oral administration. Therefore, it can not be overemphasized that the therapist must be constantly vigilant for this problem (especially during initiation of therapy) and must treat it vigorously when it occurs. Usually saline cathartics are adequate, i.e., 15 to 30 cc. of magnesia magma or 15 to 30 gm. of magnesium sulfate (Epsom salt). If these are not adequate, irritant cathartics should be tried alone or in combination with the saline cathartics. The irritant cathartics that we have found most useful are 10 to 20 cc. of elixir of carcara segrada or 15 to 30 cc. of castor oil. Some patients may respond to one cathartic but not to another.

Cholinergic agents are of value and are frequently more effective than cathartics. We have found 15 to 30 mg. of neostigmine given orally 30 minutes before each meal to be the most effective cholinergic agent for constipation. However, 5 to 10 mg. of pilocarpine or 10 mg. of bethanechol chloride (Urecholine) given before meals is also effective. Pilocarpine appears to be superior to the other cholinergic agents for combating the dry mouth which is frequently observed during mecamylamine administration.

If the constipation has progressed to ileus before adequate therapy is instituted, then the mecamylamine should be discontinued and 1 mg. of neostigmine should be given parenterally every hour until relief is obtained. If the condition is severe, standard methods for treating ileus should be employed. The danger lies with undertreatment of this complication and not with overtreatment. Case 6 is an example of a patient in whom mecamylamine produced bowel paralysis which was inadequately treated until marked ileus was present.

CASE 6.—A 50-year-old Negro man was seen with a history of hypertension for three years and which had become more severe within the past previous six months. The patient had headaches, lethargy, confusion, dyspnea, peripheral edema, and retinal hemorrhages. His blood pressure was 198/140 in the sitting position and 208/148 when standing. He had retinal hemorrhages and papilledema. The electrocardiogram showed severe myocordial damage. The blood urea nitrogen was 30 mg. per 100 cc. The patient was started on rauwolfia, without a significant effect on the blood pressure. It was felt that the patient was completely unreliable as far as following instructions was concerned, but because of the severity



13A 13B

Fig. 13A (Case 6).—Roentgenogram taken in the supine position. There is marked distention of both the large and small bowel due to ileus.

Fig. 13B (Case 6).—In the upright position multiple fluid levels are evident throughout the bowel (due to ileus).

of his disease it was decided to start mecamylamine therapy. He was started on a dose of 5 mg. twice a day, which was progressively increased so that after three weeks he was receiving 35 mg. per day (5–15–10–5). Five days later he was admitted to the hospital through the emergency room with a diagnosis of intestinal obstruction. He had a distended tender abdomen, with periumbilical pain of three days' duration. When a complete history and the roentgenograms of the abdomen became available it was decided that the patient had a fecal impaction and ileus due to the ganglionic blocking agent, mecamylamine (Figs. 13A & 13B). The blood pressure was 100/60. The blood urea nitrogen was 58 mg. per 100 cc. Fluids were administered, and 1 mg. of neostigmine (2 cc. of 1:2000) was given every hour. After the fourth dose an explosive bowel movement occurred, the blood pressure increased slowly to 120/80, and convalescence was slow but progressive over the next four days. The supine blood pressure remained normal, but the patient could not stand up, owing to orthostatic hypotension. Thereafter, this marked orthostatic effect improved and the patient's blood pressure was regulated on reserpine plus mecamylamine. The subsequent clinical course of three months' duration has been uneventful, and the blood urea nitrogen has again decreased to 28 mg. per 100 cc.

A final consideration insofar as untoward reactions are concerned is that of aggravating a preexisting renal failure. The blood urea nitrogen seems to be the best method for evaluating any untoward renal effect of blood pressure reduction. If the blood urea nitrogen is above 80 to 100 mg. per 100 cc. of blood prior to therapy, reducing the blood pressure significantly usually aggravates the renal failure. Contrariwise, when the blood urea nitrogen is normal we have not observed renal failure due to blood pressure reduction unless the pressure is reduced excessively to hypotensive levels (Case 6). If the blood urea nitrogen is only moderately elevated (40 to 60 mg. per 100 cc.), then judicious lowering of the blood pressure with a ganglionic blocking agent such as mecamylamine can be undertaken. Careful check should be kept on the blood urea

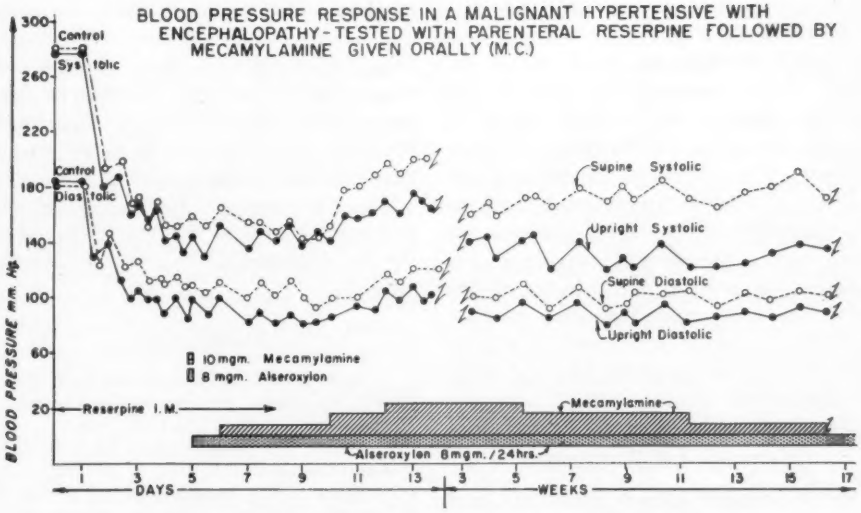


Fig. 14.—Malignant hypertension with encephalopathy. Patient was first treated with parenteral reserpine, following which he responded very well. He was then switched to oral therapy, being treated with a combination of alseroxylon and mecamylamine.

nitrogen as an index of aggravated renal failure when the effective dose of the blocking agent is reached. Usually the blood pressure can be reduced to 160-180/100-110 taken in the standing position without further compromising renal function in the patient with moderate kidney damage due to hypertension. Reducing the blood pressure below these levels must be undertaken with caution. If the blood pressure can be reduced effectively without significant depression of renal function, progressive anatomical damage due to hypertension will be arrested but not reversed.

In treating the patient who is considered a hypersensitive emergency, particularly if he is bedfast, it is usually better to administer reserpine parenterally as the initial procedure (rather than a ganglionic blocking agent), which will effectively reduce the blood pressure in such a patient, in both the supine and the upright position. This can be used as a temporary expedient for up to two weeks, following which it is necessary to set up a more permanent type of antihypertensive therapeutic program, preferably with use of the oral route of administration. A typical example is seen in Figure 14. This patient was admitted in semistupor and was very irrational. Intramuscular reserpine was administered in a dose of 10 mg. every six hours, since doses less than this seemed to be inadequate. The blood pressure decreased to mild hypertensive levels and continued within this range for a period of four days. Alseroxylon was then started in a dose of 8 mg. a day, since the patient had become rational and could take the drug by mouth. Parenteral administration of reserpine was gradually decreased over the next four days, and by the eighth day it was discontinued. On the fifth day mecamylamine was started in a dose of 5 mg. twice a day. As the effect of the intramuscular reserpine was lost, the dose of mecamylamine was gradually increased to 30 mg. a day. This proved to be adequate to maintain the blood pressure within normotensive ranges in the upright position, although in the supine position the pressure was not this well regulated. After the fifth week it was possible to reduce the mecamylamine to 20 mg. a day, and by the 11th week it could be reduced to 10 mg. a day, with adequate regulation of blood pressure. In Figure 14 one can see the

difference in the type of blood pressure reduction between parenteral reserpine and the ganglionic blocking agent, mecamylamine. With reserpine, the systolic and diastolic pressure was reduced nearly as much in the supine as in the upright position. When the effect of the parenteral reserpine was lost and the mecamylamine became the predominantly effective agent, one sees that there was a progressive increase in the supine blood pressure but that the upright blood pressure remained reduced, a reflection of the primary orthostatic blood pressure effect of the ganglionic blocking agent, mecamylamine.

Summary and Conclusions

Results obtained in the treatment of hypertension with mecamylamine, a ganglionic blocking agent, which is completely absorbed from the intestinal tract, are reviewed. The patients were treated as ambulatory patients.

The drug is an effective agent for reducing the blood pressure in patients with severe hypertension. Because of its complete oral absorption, it is more predictable from day to day, and dosage is easier to titrate, since the oral and parenteral route of administration can be used interchangeably with the same dose.

The side-effects with mecamylamine are similar, both qualitatively and quantitatively, to those observed with other available ganglionic blocking agents such as hexamenthonium and pentolinium. The effect of reducing salivation is more marked with mecamylamine than with the other blocking agents, and the initial effect of reducing intestinal peristalsis may be more marked than with other blocking agents.

The pharmacology and specific clinical problems relative to the use of this drug for the treatment of hypertension are reviewed.

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Treatment in Internal Medicine

RHEUMATIC FEVER

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THERE is no specific treatment for rheumatic fever. Much can be done, however, to help the patient. The exact pathogenesis of rheumatic fever remains unknown, but there is no longer serious doubt that it develops as a complication of infection with Group A streptococci. Highly effective antibiotic therapy has made control of streptococcal infection in rheumatic subjects feasible. Furthermore, the availability of nonspecific but highly potent anti-inflammatory agents such as salicylates and the adrenal cortical hormones affords the means of controlling the toxic manifestations of the disease in most cases. In my opinion the proper administration of these agents is a valuable aid in the management of the acute stage of the disease even though there is no definite evidence that the ultimate degree of cardiac damage sustained can be reduced. This discussion makes no attempt to review the voluminous literature on the treatment of rheumatic fever. It presents, rather, my current approach to the practical management of this disease and acknowledges that the limitations to our understanding of the disease process inevitably result in wide variations in therapeutic approach.

Antistreptococcal Therapy

There is general agreement on one aspect of treatment. Group A streptococci that may linger in the pharynx of the patient with acute rheumatic fever as a result of the antecedent infection must be eradicated, and new streptococcal infection must be prevented. Though throat cultures may not reveal the presence of these organisms (and several cultures of the throat should be made before treatment is initiated), it is wise to proceed as though the organisms were present deep in the lymphoidal tissues of the pharynx. Cultures of tonsils removed from patients are often positive for Group A streptococci even though prior culture of the intact mucosa of the pharynx fails to reveal these organisms.[1]

To achieve bacteriologic cure of streptococcal pharyngitis or of the carrier state, it is necessary to provide penicillin for a minimum period of 10 days. Because of the exquisite sensitivity of the organisms to penicillin, large doses are unnecessary. Doses of penicillin that maintain blood levels of about 0.04 unit per cubic centimeter of serum are quite as effective as any higher dose if such levels are maintained for 10 days. Furthermore, higher blood levels do not result uniformly in permanent bacteriologic cure when they are maintained for any period less than 10 days.[2]

For this reason, a single intramuscular injection of 600,000 to 1,200,000 units of a long-acting depot penicillin salt, benzathine penicillin, has been shown to achieve as high a rate of bacteriologic cure as any other course of penicillin employed for the treatment of uncomplicated streptococcal pharyngitis.[3] Such single intramuscular injections of benzathine penicillin result in low but persistent and adequate blood levels of penicillin for at least 10 days.[4] The same results may be achieved with more frequent injections of other penicillin salts. Procaine penicillin G in 2% aluminum monostearate in oil, 600,000 units administered intramuscularly every third day for three or four doses, or daily intramuscular injections of 300,000 to 600,000 units of aqueous procaine penicillin G for 10 days, may be administered as alternative therapy. In my

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opinion there is no advantage to these more frequent injections and no less risk of hypersensitivity than that involved with the use of benzathine penicillin.

Once Group A streptococci have been cleared from the throat, continuous prophylaxis against new infection is instituted. A variety of methods are suitable for this purpose.[5] Small daily oral doses of penicillin G (200,000 units once or twice daily) or of sulfadiazine (1.0 gm. daily) may be employed. In my experience, however, a single monthly injection of 1,200,000 units of benzathine penicillin avoids the uncertainty of poor patient cooperation and has been found to be extremely effective in preventing rheumatic recurrences and new streptococcal infection, especially during the first two years of convalescence, when the risk of rheumatic recurrences is greatest.[6] A full discussion of prophylaxis of rheumatic recurrences is beyond the scope of this paper, and for a more complete discussion the reader is referred to recent reviews.[7]

Anti-Inflammatory Treatment

There is no evidence that treatment with either salicylates or adrenocortical hormones modifies the duration of the rheumatic attack. In both cases the effect of these agents is to suppress the inflammatory process. Whether intensive suppression of cardiac inflammation results in diminished scarring of cardiac tissues is a question that is still debated. Controlled studies of fixed doses of acetylsalicylic acid, corticotropin (ACTH), and cortisone, respectively, administered for a fixed period of six weeks, have not shown so far that any one of these agents is superior in reducing the incidence of clinically apparent rheumatic heart disease one year after termination of therapy.[8] These studies have been criticized by some on the basis of inadequacy of dosage and duration of administration of hormones. Several recent studies have purported to show favorable results in patients with initial attacks of rheumatic carditis treated early (within the first two weeks) in the course of the disease with very large doses of cortisone for prolonged periods.* The absence of adequate controls, the extreme variability of the course of rheumatic fever, the limited numbers of cases of this type available for study, and the risks attendant in the prolonged administration of large doses of hormones have prompted caution and conservatism in the general acceptance of this therapeutic approach for all rheumatic fever patients.

Selection of Anti-Inflammatory Agent

Salicylates.—Pending the availability of further data, it may be reasonable to employ a therapeutic approach that is adapted to the nature of the individual case. It has been shown that approximately 90% or more of patients with acute rheumatic fever, who have no clinical evidence of carditis during the acute stage of the disease, recover from the episode without evident rheumatic heart disease one year later.[8] These are usually patients with the acute polyarthritis of rheumatic fever. For such patients therapy may be initiated with large doses of salicylates. An initial dose of 10 gm. (150 grains) of acetylsalicylic acid per day is administered to patients weighing 70 kg. (150 lb.) or more, and proportionately smaller doses are administered to patients weighing less (a convenient formula is 1 grain (60 mg.) per pound per day). This is administered in divided doses every four hours. Small amounts of milk taken with each dose reduce gastric irritation. Large doses of sodium bicarbonate interfere with absorption and should be avoided. These doses of acetylalicylic acid are continued until a satisfactory clinical response is obtained, that is, until the patient has complete relief of symptoms and signs of arthritis and until the temperature returns to normal or nearly normal range. Thereafter the dose may be reduced daily to two-thirds the initial value and maintained until all laboratory manifestations of inflammatory disease have returned to normal (see below). Subse-

* References 9-11.

quently the dose may be reduced to one-half the initial daily dose for the remainder of the course of therapy. Should clinical or laboratory evidence of relapse occur when the doses are reduced, it is advisable to return to the previous higher dose that "controlled" the process.

Toxic manifestations are common with the use of large doses of salicylates, and these may force a reduction in dose before the response is adequate. If control of the inflammatory state is not adequate on lower, subtoxic doses, the substitution or addition of another agent should be considered. Of particular importance is the toxic symptom of hyperpnea, which may be insidious and may lead to serious respiratory alkalosis and eventually metabolic acidosis if undetected. Frequent determinations of serum pH and carbon dioxide content are helpful in this regard. Inasmuch as the absorption of salicylate varies considerably from patient to patient, determination of salicylate blood levels is useful, particularly if the patient does not appear to respond well to treatment. The usual serum level at which most patients appear to respond is between 20 and 40 mg. per 100 cc.

Some patients are quite intolerant of salicylates and have intense gastric irritation with even small doses or develop salicylism at relatively low blood levels. In such patients aminopyrine may be employed. It is, in fact, a highly effective drug, equivalent in antirheumatic activity to acetylsalicylic acid in approximately one-fifth the daily dose of the latter. The total and differential white blood cell count should be observed at weekly intervals when aminopyrine is employed.

There should be no hesitancy in adding or substituting cortisone or one of its analogues when it is apparent that salicylates are not providing satisfactory control of the inflammatory process. In my experience cortisone is frequently a more potent agent

SUPPRESSIVE THERAPY IN CHRONIC RHEUMATIC CARDITIS

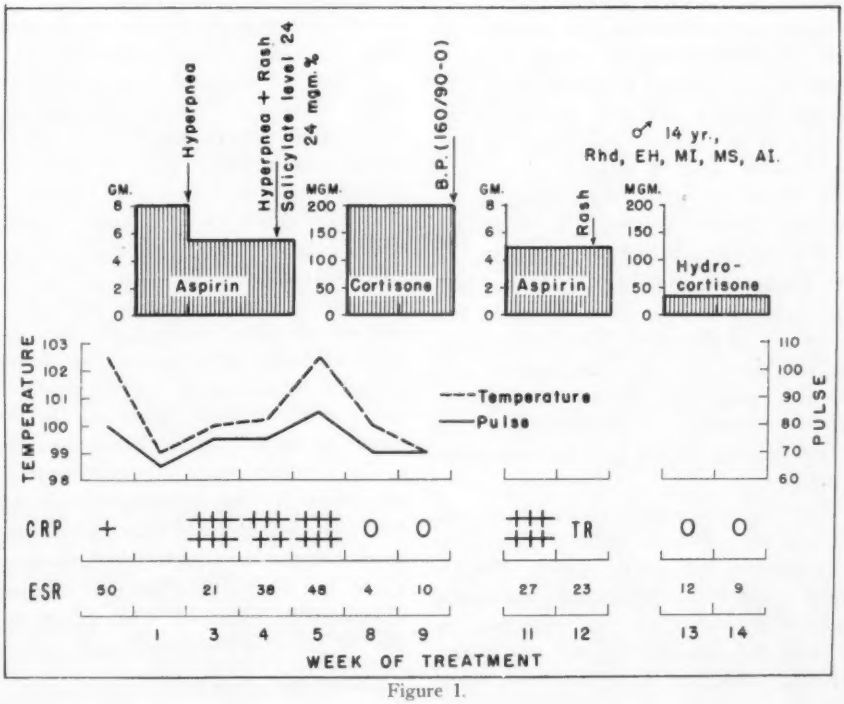

Figure 1.

than salicylates in suppressing rheumatic inflammation and salicylates alone often fail to control the disease at subtoxic doses. A typical instance is demonstrated. (Fig. 1).

Cortisone and Its Analogues

For the patient with clinically apparent active rheumatic carditis, who has a severer form of the disease, treatment may be initiated with relatively large doses of cortisone or one of its analogues. No arbitrary dosage of the hormone can be recommended. Cortisone may be administered orally in initial doses of 300 mg. daily (usually in four divided doses) until a good clinical response is achieved. Thereafter, 200 mg. may be administered daily for several more weeks depending upon the patient's response and the severity of the disease. It would appear logical to administer enough hormone to reverse manifestations of active inflammation, such as the presence of C-reactive protein in blood and elevation of erythrocyte sedimentation rate, as well as the acute toxic clinical manifestations, such as fever, tachycardia, and polyarthritis. As with salicylates, treatment should be maintained for a minimum period of six weeks, but the duration should be guided by the severity of the disease and should be prolonged when signs of relapse appear upon reduction of dosage. Fewer relapses are encountered when treatment is maintained for 9 to 12 weeks rather than 6 weeks.

It is important to reduce the dose of hormone gradually over a period of about two weeks and to recognize that abrupt cessation of treatment leaves the patient in a state of temporary adrenal insufficiency, due to suppression of endogenous adrenal cortical activity during prolonged hormone therapy.

Hydrocortisone may be used in place of cortisone in a dose of about two-thirds to three-quarters that of the latter. The recently synthesized compound prednisone (metacortandracin) is as effective as cortisone and has less sodium- and water-retaining properties. It is preferred, therefore, for patients with severe carditis and congestive heart failure. The dosage is about one-fifth that of cortisone. The halogenated cortisone analogues, fludrocortisone and chlorhydrocortisone, are about 10 times as potent as cortisone per unit weight but have greater sodium- and water-retaining properties and are therefore unsuitable for patients with carditis. Corticotropin is as effective as cortisone but has the disadvantage of necessitating parenteral administration. It may be administered in initial doses of 120 mg. daily by injection and gradually reduced thereafter according to the manner suggested for the use of cortisone.

The relative anti-inflammatory potency of the various adrenal cortical compounds can be assayed by their ability to reverse the test for C-reactive protein (CRP) in the blood. This abnormal protein appears in the blood in response to a variety of inflammatory stimuli and is a sensitive but entirely nonspecific indicator of rheumatic inflammation.† With adequate suppression of the inflammatory process, it disappears from the blood within a few days to one week, and, conversely, it reappears promptly when suppressive therapy is inadequate. Although it usually parallels the behavior of the sedimentation rate, it varies more promptly than the latter with variations in the clinical course of the disease. Moreover, when congestive heart failure is present the sedimentation rate is often depressed to low values, whereas CRP is unaffected by this complication. Its disappearance from the blood following adrenal cortical hormone or salicylate therapy is not the result of a direct effect of these agents on the metabolism of the C-reactive protein but appears to be a reflection of the effectiveness of suppression of the inflammatory process.[14] The relative potency of four different cortisone analogues in a patient with chronically active and protracted rheumatic carditis is illustrated in Figure 2. This graph shows the "titration" of the dose of each compound

† References 12 and 13.

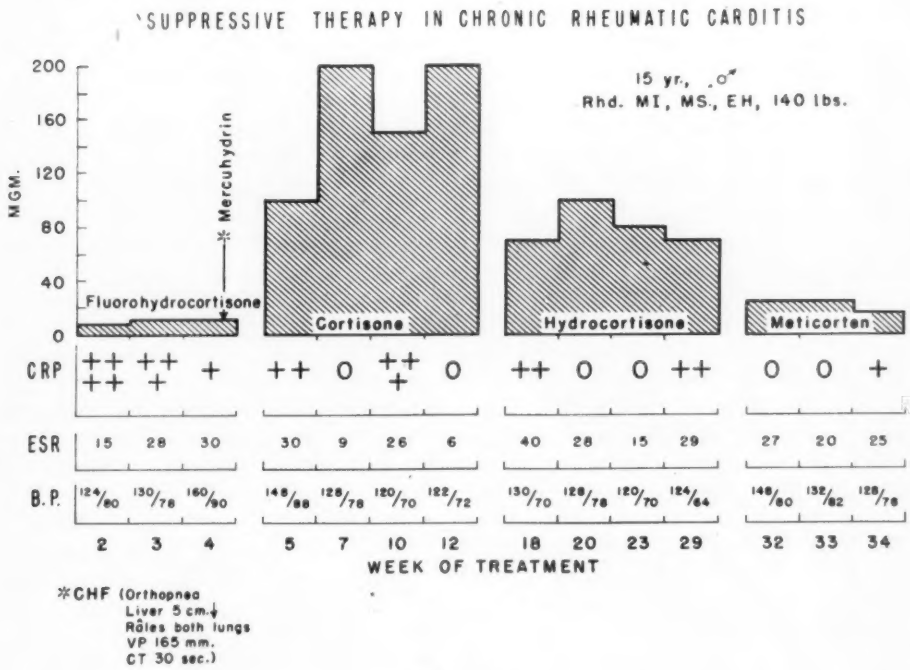

Figure 2

required to cause the disappearance of CRP from blood.

During treatment it is helpful to make weekly determinations of the erythrocyte sedimentation rate, C-reactive protein, hematocrit value, and white blood cell count. Electrocardiograms and a teleroentgenogram are also taken weekly. The latter is particularly useful to detect change in heart size. Pericarditis is notoriously difficult to detect by physical signs and is often overlooked unless x-ray films of the chest are made at regular intervals. Such films also help to reveal pulmonary infection, which may otherwise be masked by cortisone therapy.

Management of the Side-Effects of Adrenal Cortical Hormone Therapy

The undesirable side-effects of treatment with corticotropin or cortisone are manifestations of excessive adrenal cortical stimulation. They consist of the following signs and symptoms: disturbances in electrolyte, water, and carbohydrate metabolism; skin changes such as acneiform eruption, hirsutism, abdominal striae, and pigmentation; unusual fat deposition, especially around the face (moon facies), base of the neck, breasts, abdomen, and hips; amenorrhea; hypertension; enlarged fatty liver; leucocytosis, and cerebral changes. When treatment is discontinued, all of these side-effects disappear. Retention of sodium and water may be diminished by restricting sodium chloride intake sharply: This is particularly important when large doses of cortisone are administered to patients with carditis. In such cases it is helpful to employ special diets which have been devised to reduce the intake of sodium chloride to less than 100 mg. per day.

Mercurial diuretics may have to be employed in patients with congestive heart failure. To compensate for possible loss of potassium, 2 to 3 gm. of potassium chloride should be given daily. The urine should

be tested for sugar frequently, since diabetes, known or potential, becomes temporarily intensified and insulin requirement is increased. The diet should be high in protein to counteract the negative nitrogen balance sometimes induced by the hormones. Patients who are, or who have been, emotionally unstable or psychoneurotic are more likely to develop mental and emotional disturbances than those with stable personalities. It should also be borne in mind that cortisone and corticotropin have the capacity to mask pain and symptoms and signs of peritonitis and to suppress fever. An infectious or suppurative process may therefore be overlooked unless the physician is alert to the possibilities of its presence.

Daily blood pressure determinations will detect the not uncommon complication of hypertension, which may require reduction in dose of hormone and addition of salicylates to assist in suppression of the inflammatory process.

Combined Treatment with Salicylates and Hormones

There is little objection to the use of both agents simultaneously, and, indeed, some authorities advise combined therapy, arguing that maximal suppression of inflammation by all available means may be logical. The use of salicylates is of particular value during the final weeks of withdrawal of hormone therapy to aid in suppression of mild relapse of low-grade rheumatic activity. I prefer to initiate therapy with one agent. If prompt and adequate control of the inflammatory process is achieved with hormones or salicylates, there is no definite evidence as yet that the addition of another agent will produce superior results.

The Use of Digitalis for Treatment of Heart Failure

Some authorities state that digitalis is of little value in the treatment of heart failure in patients with rheumatic carditis and that it is, in fact, contraindicated because of the frequency with which toxic manifestations develop with its use in this situation. In my experience digitalis usually improves cardiac function except in instances of very severe myocardial inflammation. Furthermore, the use of the rapidly excreted glycosides, such as digoxin, results in the patient's prompt recovery from digitalis toxicity if medication is discontinued at the first signs of toxic manifestations. It is often difficult to decide whether the appearance of an arrhythmia, such as auricular fibrillation, or frequent ventricular premature contractions, is the result of digitalis toxicity or myocarditis. Discontinuance of digoxin is usually followed by the disappearance of toxic manifestations within 24 to 48 hours if the disturbance is due to the drug.

For the adult or adolescent of average weight, 1.0 mg. of digoxin is administered initially. Thereafter 0.5 mg. is given by mouth every 6 to 12 hours until a therapeutic response is obtained or until a total dose of 2.5 to 3.0 mg. is administered. If no response is obtained, the dose is increased further cautiously until either improvement or toxic manifestations supervene. Once an adequate dose is given digitalization is usually maintained by 0.25 to 0.5 mg, administered daily. Doses may be proportionately lower in younger children, but no arbitary weight-dose ratio is applicable for digitalization. Some children weighing 60 to 100 lb. require the same dosage as outlined above for the adult. Throughout digitalization care is taken to administer adequate daily amounts of potassium, especially when the patient receives cortisone and when mercurial diuretics are used freely.

In evaluating the effect of cortisone or its analogues upon heart failure it is well to remember that cardiac compensation that occurs while the patient is also receiving digitalis can be due to the latter rather than to the former. For this reason, in clinical investigation of the effect of hormones upon

heart failure in rheumatic fever, it has been our policy to withhold digitalis or to use it alone before hormone therapy is introduced. Many reports in the literature on the salutary effect of adrenocortical hormones upon heart failure have not taken account of the concurrent digitalization of the patient. An example of the striking improvement in cardiac function that may occur with the use of digitalis is shown in Figure 3. This

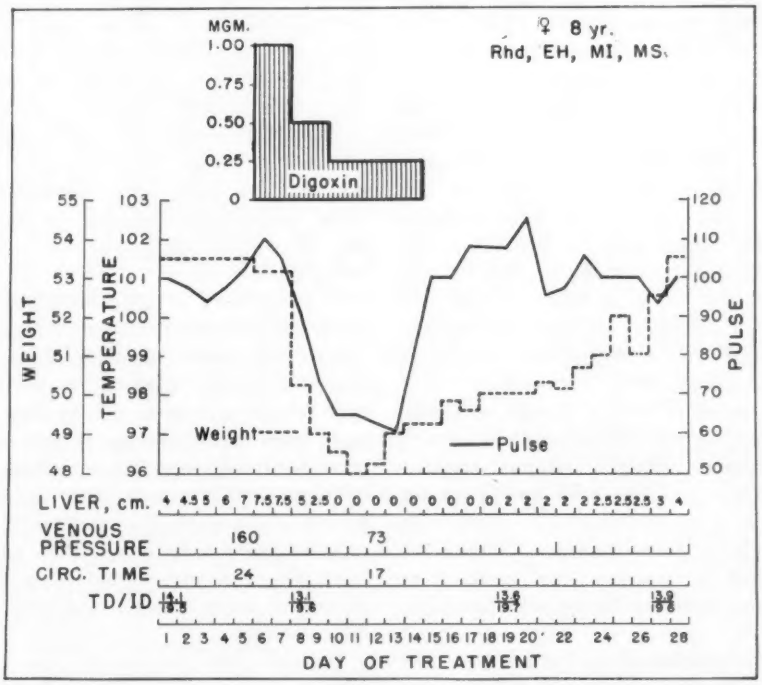

Figure 3

8-year-old girl responded dramatically to digoxin, exhibiting a marked diuresis, weight loss, decrease in liver enlargement and tenderness, decrease in venous pressure and circulation time, and disappearance of edema, dyspnea, and orthopnea. There were unequivocal signs of acute rheumatic fever when digoxin was administered (recent fever, polyarthritis, positive C-reactive protein and elevated sedimentation rate, changing murmurs, and enlarging heart). When digoxin was withheld, most signs of congestive heart failure reappeared.

To be sure, this is an unusually striking demonstration of the effectiveness of digitalis, and other patients who show relatively little response could be selected for presentation also. Improvement is frequent enough, however, so that digitalis should be employed whenever heart failure is encountered, particularly in patients with advanced rheumatic heart disease, where mechanical factors contribute to the problem of cardiac decompensation. In the absence of signs of heart failure there is, of course, no reason to use digitalis. When clinical signs are due solely to pericardial effusion or to severe obstruction of the mitral valve, no response to digitalis can be expected.

Treatment of Sydenham's Chorea

The response of the symptoms of Sydenham's chorea to the anti-inflammatory reagents is difficult to evaluate because of the extreme variability of the course of this

syndrome and the frequent spontaneous rapid recovery of the patient. Neither the adrenal cortical hormones nor salicylates have been impressive, in my opinion. When constitutional signs of rheumatic inflammation (fever, anemia, anorexia, malaise) are concomitantly present, or when carditis or other rheumatic manifestations are active, anti-inflammatory drugs should be used, inasmuch as the suppression of such inflammation has a beneficial effect upon choreiform activity. Patients with so-called "pure" chorea, a syndrome that often occurs late in the rheumatic attack, when inflammatory signs have disappeared,[15] fail to respond well to cortisone or salicylates. Indeed, I have been discouraged by severe psychotic episodes in three patients with chorea who were treated with cortisone. Although chorea may be associated with psychotic reactions in the absence of such therapy, the beneficial effects of the hormones are equivocal, and they are not recommended unless concurrent carditis or systemic inflammation is present.

The course of chorea, though sometimes prolonged, is self-limited. Patient nursing care, adequate sedation, and good nutrition usually are associated with good response. The use of diphenhydramine (Benadryl), Rauwolfia, chlorpromazine (Thorazine), and fever therapy have not produced an impressive response, in my experience.

Ambulation of the Patient and Evaluation of Subsidence of the Rheumatic Attack

During the acute stage of the disease, and while anti-inflammatory agents are being administered, patients are usually kept in bed. How strictly bed rest is enforced depends upon the severity of the attack, the degree of cardiac involvement, and the effectiveness of therapy. Patients who have no clinical evidence of carditis and who respond promptly to anti-inflammatory agents are often permitted bathroom and chair privileges. Sedentary group activities and occupational therapy may be more beneficial than strictly enforced bed rest that creates restlessness and boredom. In the presence of severe cardiac involvement or symptoms of diminished cardiac reserve a more conservative attitude toward rest is enforced.

When hormone or salicylate therapy is gradually withdrawn and no clinical evidence of relapse appears, progressive ambulation is started. This should be cautious if laboratory evidence of relapse, such as rise in erythrocyte sedimentation rate (ESR) and appearance of CRP in blood is noted. Reappearance of laboratory signs of inflammation after 6 to 12 weeks of treatment may represent but a transient relapse (the so-called "rebound") and may disappear in one to two weeks. If they persist longer, however, it is advisable to reinstitute treatment for an additional four to six weeks and to continue to restrict the patient to sedentary activity.

If all evidence of inflammation is absent upon the withdrawal of hormones or salicylates, the patient should continue to be observed closely, inasmuch as the disease may relapse as long as five to eight weeks later, even in the absence of new streptococcal infection. Such delayed relapses after withdrawal of treatment occur within four to five weeks in 95% of patients.[16] Later relapses are usually noted when advanced heart disease is present and when the subsidence of active carditis cannot be judged with accuracy.

Beyond this two-month convalescent period, new attacks of rheumatic fever do not seem to occur in the absence of another streptococcal infection.[16] The patient's resumption of normal activity is conditioned, therefore, by the degree of cardiac involvement. For the first six months after the attack competitive games or severe exertion are discouraged. Thereafter, if the heart is normal, restrictions are withdrawn. If an organic murmur is present but the heart is not enlarged, and no signs of diminished cardiac reserve are noted following a year's observations, restrictions are often lifted. An exception may be the patient with pronounced aortic insufficiency or mitral in-

sufficiency. Here, evidence of severely mechanically handicapped valves warrants restriction of activity as a prophylactic measure, even in the absence of marked enlargement of the heart or diminished cardiac reserve.

Occasionally it is observed that Sydenham's chorea or erythema marginatum appears late in convalescence as an isolated manifestation, without evidence of constitutional inflammatory signs, such as elevation of ESR or appearance of CRP in blood. This may occur as long as several months after the apparent subsidence of the rheumatic attack, even in the absence of new streptococcal infection.[15] The patient should be under close observation, therefore, and examined carefully at least at monthly intervals during the first year following the attack. Thereafter, however, I have not observed the appearance of chorea or of erythema marginatum in patients receiving careful prophylaxis unless there has been a "breakthrough" of streptococcal infection.[16]

About 5% of patients with acute rheumatic fever develop a more chronic protracted form of the disease. Especially in those with advanced heart disease, it is difficult to know when clinically active rheumatic carditis has abated. It is not uncommon, however, to note a striking improvement in general health, disappearance of tachycardia, and recovery of apparently unlimited cardiac reserve in young patients who have suffered a prolonged rheumatic episode and who have had long-standing rheumatic heart disease. This recovery may take place in the absence of change in heart size or change in murmurs. It is a good prognostic sign for the end of the rheumatic attack. If recurrences are prevented in such patients, it is unusual for signs of cardiac decompensation to appear without a new rheumatic attack until many years later, when myocardial failure may supervene as a result of mechanical factors.

Summary

In the absence of a specific cure for rheumatic fever, there are many therapeutic measures which reduce the severity of the acute attack and improve the patient's chances for recovery and longevity.

Prompt eradication of Group A streptococci and continuous prophylaxis against subsequent infection with this organism is perhaps the most important single measure. Also helpful, however, is adequate suppression of the inflammatory process with either salicylates, the adrenal cortical hormones, or both. The least such therapy does is to improve the patient's general condition and reduce the toxic manifestations of the disease that can be harmful and dangerous to the patient with severe carditis. The evidence for a modifying effect of the antirheumatic agents upon ultimate cardiac damage is equivocal but suggestive.

The proper control of side-effects of treatment, careful treatment of heart failure with digitalis and diuretics, and the management of the patient's activity are all important supportive measures.

Under such management the prognosis for the patient with acute rheumatic fever has been improving steadily.

The graphs used in this paper were prepared by Dr. William Lynch and were based upon data obtained from patients studied at Irvington House, Irvington-on-Hudson, New York.

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THE MANIFESTATIONS AND TREATMENT OF POISONING DUE TO NERVE GAS AND OTHER ORGANIC PHOSPHATE ANTICHOLINESTERASE COMPOUNDS

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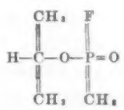
THE NERVE gases are a group of highly toxic organic esters of phosphoric acid derivatives which have physiologic effects attributable to the inhibition of cholinesterase enzymes. The effects resemble those produced by physostigmine and neostigmine (Prostigmin) but are more intense and more prolonged. The nerve gases are among the most toxic of the chemical warfare agents, and they are the most adaptable to long-range attack, as upon civilian populations.[1] A number of related but somewhat less toxic organic phosphate anticholinesterase compounds have proved to be useful in medicine and in agriculture. Diisoprophyl fluorophosphate (DFP) has been studied in detail * and has been employed as a therapeutic agent in the management of abdominal distention,† urinary retention, and glaucoma.[6] Tetraethylpyrophosphate (TEPP) [7] and octamethyl pyrophosphoramide (OMPA) [8] proved to be of some value in the management of myasthenia gravis, but they have been replaced by less potent anticholinesterase compounds. Parathion, bis-(monoisopropylamino)-fluorophosphine oxide (Mipafox), hexaethyltetraphosphate (HETP), and TEPP have been widely used throughout the world as insecticides, and their indiscriminate dispersal has resulted in a number of instances of poisoning, some of them fatal.‡ The symptoms of poisoning by these compounds are similar to those of the nerve gases, and the measures recommended below for the management of nerve-gas poisoning are also recommended for the management of poisoning due to other organic phosphate anticholinesterase compounds.

The nerve gases include sarin § (isopropyl methyl phosphonofluoridate), tabun (dimethylamido-ethoxyphosphoryl cyanide), and several other organic esters of phosphoric acid derivatives.‖ The effects of nerve-gas poisoning described below are those that have been observed in man following exposure to sarin.¶ It is believed that the effects of tabun and of the other nerve gases would be, in general, similar to those of sarin.



Physical Properties

The nerve gases are colorless to light brown liquids, most of which are volatile at ordinary temperatures. While some have a faint sweetish fruity odor, this is not sufficiently intense or distinctive to enable detection under field conditions. They react slowly with water and rapidly with strong alkali, yielding hydrolysis products which are either nontoxic or less toxic than the agents themselves. Following a single bomb burst or spray some of the nerve gases persist in toxic concentrations for many hours, while others persist only until the cloud has been dissipated, which is usually within about 10 minutes.

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* References 2-5.

† References 2-5.

‡ References 9-11.

§ The structural formula of sarin, which has also been designated GB, is

‖ References 12-13.

¶ References 14-17.

Absorption

The nerve gases may be absorbed through any body surface. When dispersed as a vapor, spray, or aerosol, or adsorbed on dust, they are readily absorbed through the respiratory tract or conjunctivae, while liquid nerve gases, or solutions, may be absorbed through the conjunctivae, skin, or gastrointestinal tract. The nerve gases produce local effects on the tissue through which absorption occurs, particularly on the respiratory tract and eyes, and, if absorption is sufficiently great, this is followed by generalized systemic effects. The respiratory tract is the most rapid and most complete of these routes of absorption.

TABLE 1.—*Signs and Symptoms of Nerve-Gas Poisoning*

Site of Action	Signs and Symptoms
	Following Local Exposure
Muscarine-like	
Pupils	Miosis, marked, usually maximal (pin-point), sometimes unequal
Ciliary body	Frontal headache, eye pain on focusing, slight dimness of vision, occasional nausea and vomiting
Conjunctivae	Hyperemia
Nasal mucous membranes	Rhinorrhea, hyperemia
Bronchial tree	Tightness in chest, sometimes with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, cough
Sweat glands	Sweating at site of exposure to liquid
Nicotine-like	
Striated muscle	Fasciculations at site of exposure to liquid
	Following Systemic Absorption
Muscarine-like	
Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, dyspnea, slight pain in chest, increased bronchial secretion, cough, pulmonary edema, cyanosis
Gastrointestinal	Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness (? cardiospasm) with "heartburn" and eructation, diarrhea, tenesmus, involuntary defecation
Sweat glands	Increased sweating
Salivary glands	Increased salivation
Lacrimal glands	Increased lacrimation
Heart	Slight bradycardia
Pupils	Slight miosis, occasionally unequal, later more marked miosis
Ciliary body	Blurring of vision
Bladder	Frequency, involuntary micturition
Nicotine-like	
Striated muscle	Easy fatigue, mild weakness, muscular twitching, fasciculations, cramps, generalized weakness, including muscles of respiration, with dyspnea and cyanosis
Sympathetic ganglia	Pallor, occasional elevation of blood pressure
Central nervous system	Giddiness; tension; anxiety; jitteriness; restlessness; emotional lability; excessive dreaming; insomnia; nightmares; headache; tremor; apathy; withdrawal and depression; bursts of slow waves of elevated voltage in EEG, especially on overventilation; drowsiness; difficulty concentrating; slowness of recall; confusion; slurred speech; ataxia; generalized weakness; coma, with absence of reflexes; Cheyne-Stokes respiration; convulsions; depression of respiratory and circulatory centers, with dyspnea, cyanosis, and fall in blood pressure

Effects (Table 1)

Mechanism of Action

The effects of the nerve gases are due entirely to their ability to inhibit cholinesterase enzymes throughout the body. Since the normal function of these enzymes is to hydrolyze acetylcholine wherever this compound is liberated, such inhibition results in the accumulation of excessive concentrations of acetylcholine at the various sites of action. These include the endings of the parasympathetic nerves to the smooth muscle of the iris, ciliary body, bronchial tree, gastrointestinal tract, bladder, and blood vessels; parasympathetic nerves to the secretory glands of the respiratory tract and to cardiac muscle, and sympathetic nerves to the sweat glands. The accumulation of acetylcholine at these sites results in characteristic "muscarine-like" signs and symptoms (Table 1). The accumulation of acetylcholine at the endings of motor nerves to voluntary muscle and in the autonomic ganglia results in "nicotine-like" signs and symptoms. Finally, the accumulation of excessive concentrations of acetylcholine in the brain and spinal cord results in characteristic central nervous system symptoms. The inhibition of cholinesterase enzymes throughout the body by nerve gas rapidly becomes more or less irreversible, so that the effects of these compounds are prolonged. Until the tissue cholinesterase enzymes are restored to normal activity,

probably by their regeneration over a period of days or weeks, there is a period of increased susceptibility to the effects of another exposure to any of the nerve gases. During this period the effects of repeated daily exposures by any route are cumulative.

Effects of Nerve Gas Vapor

Within a few minutes after exposure to vapor there appear local effects on the smooth muscle of the eye and respiratory tract and on the secretory glands of the latter. If the concentration of vapor is sufficiently great, the nerve gas is rapidly absorbed by the respiratory tract and carried by the circulation throughout the body, resulting in widespread systemic effects.

Local Ocular and Respiratory Effects.—These begin within one to several minutes after exposure, before there is any evidence of systemic absorption. The earliest ocular effect which follows minimal symptomatic exposure to vapor is pupillary constriction. This is an invariable sign of ocular exposure to a concentration of vapor sufficient to produce symptoms, and it is also the last ocular manifestation to disappear. The pupillary constriction may be unequal. Within a few minutes after the onset of exposure there also occur conjunctival hyperemia and a sensation of pressure and heaviness in and behind the eyes. Vision is usually not grossly impaired, but there may be slight dimness, especially in the peripheral fields and in dim or artificial light. The earliest effects on the respiratory tract following minimal exposure are a watery nasal discharge, nasal hyperemia, a sensation of tightness in the chest, and, occasionally, prolonged wheezing expiration, suggestive of bronchoconstriction or increased bronchial secretion. Approximately four times the minimal symptomatic exposure results in extreme miosis, aching in and behind the eyes, difficulty in accommodation, and severer rhinorrhea and frontal headache. The aching, which is atributable to ciliary spasm, becomes worse when one attempts to focus or looks at a bright light. Some twitching of the eyelids may occur. There is also intermittently more marked tightness in the chest, and there may be some cough. Occasionally there is nausea and vomiting, which, in the absence of systemic absorption, may be due to a reflex initiated by the ocular effects. These local effects may result in moderate discomfort and some loss of efficiency, but they do not produce serious incapacitation. Following minimal symptomatic exposure the miosis lasts about 24 hours and the rhinorrhea lasts a few hours. After four times the minimal symptomatic exposure miosis is well established within half an hour, remains maximal for at least 24 hours, and then diminishes gradually over a period of 3 to 14 days. The conjunctival suffusion, eye pain, and headache may last up to two to five days. The rhinorrhea usualy lasts for several hours after minimal exposure and for about one day after severer exposure. The respiratory symptoms are usually intermittent and of several hours' duration after mild exposure, and they may last for one to two days after severer exposure.

Systemic Effects.—After approximately six times the minimal symptomatic exposure sufficient absorption of nerve gas occurs to produce not only severer local ocular and respiratory effects but also systemic effects. The resulting symptoms are severe enough to produce some casualties. After 15 to 20 times the minimal symptomatic exposure the effects became alarming, and all unprotected persons are seriously incapacitated. The time interval between the exposure and onset of systemic effects depends upon the degree of exposure. Systemic symptoms may begin within half an hour after mild exposure or within a few minutes after moderate exposure. Following inhalation of nerve gas, respiratory symptoms begin before the systemic effects, but the other muscarine-like symptoms may develop concomitantly with the nicotine-like and central nervous system effects. Mild systemic effects generally last for several hours. Moderately severe

symptoms remain at maximal severity for 6 to 24 hours and then diminish gradually over a period of one to six days. During the period of recovery symptoms may recur intermittently, especially following exertion. The lethal exposure, in the absence of treatment, is estimated to be approximately 30 to 50 times the minimal symptomatic exposure.

Muscarine-like Effects: The "tightness" in the chest, which is an early local symptom, increases as the nerve gas is absorbed into the systemic circulation. After moderate or marked exposure, excessive bronchial secretion occurs, and this may become very profuse, causing coughing, airway obstruction, and respiratory distress. Audible wheezing may occur, with prolonged expiration and difficulty in moving air into and out of the lungs, owing to increased bronchial secretion or bronchoconstriction, or both. There may be some pain referred to the lower thorax. Increased salivation occurs. The bronchial secretion and salivation may be so profuse that watery secretions run out of the sides of the mouth. If postural drainage or suction are not employed, airway obstruction and pulmonary edema may ensue. Laryngeal spasm may add to the respiratory difficulties. If the upper airway becomes obstructed by secretions or by laryngeal spasm, or if the bronchial tree becomes obstructed by secretion or bronchoconstriction, little ventilation may occur in spite of respiratory movements. The casualty may gasp for breath, froth at the mouth, and become cyanotic. He may be seized with panic in his struggle for air, thrash about, and then fall unconscious. Following inhalation of nerve gas vapor the respiratory manifestations predominate over the other muscarine-like effects, and they are likely to be severest in older persons and in those with a history of respiratory disease, particularly bronchial asthma. However, if the exposure is not so overwhelming as to cause death within a few minutes, other muscarine-like effects appear. These include sweating, anorexia, nausea, and epigastric and substernal "tightness" (probably due to cardiospasm) with "heartburn" and eructation. If absorption of nerve gas has been sufficiently great, whether due to a single exposure or to repeated smaller exposures, there may follow abdominal cramps, increased peristalsis, vomiting, diarrhea, tenesmus, increased lacrimation, urinary frequency, and occasionally, slight bradycardia. The casualty becomes bathed in sweat, and he may have involuntary defecation and urination.

Nicotine-like Effects: With the appearance of moderate muscarine-like systemic effects the casualty begins to have increased fatigability and mild generalized weakness which is increased by exertion. This is followed by involuntary muscular twitching, scattered muscular fasciculations, and sometimes muscle cramps. There may be pallor of the skin and moderate elevation of the blood pressure, due to vasoconstriction resulting from cholinergic stimulation of sympathetic ganglia and possibly from the release of epinephrine. If the exposure has been sufficiently marked, the fascicular twitchings, which usually appear first in the eyelids and in the facial and calf muscles, become generalized. Innumerable rippling movements are seen under the skin, and twitching movements appear in all parts of the body. This is followed by severe weakness, which is generalized and includes the muscles of respiration. The respiratory movements become more labored, shallow, and rapid; then slow, and finally intermittent. The exchange of air, which has already been interfered with as a result of increased bronchial secretion, bronchoconstriction, and laryngeal spasm, is further reduced, and cyanosis increases. Weakness of the muscles of the tongue and pharynx may aggravate upper airway obstruction. The weakness of the respiratory muscles may become so profound that all respiratory efforts cease, and death occurs within a few minutes unless artificial respiration is promptly instituted.

Central Nervous System Effects: The

earliest systemic manifestations of nerve gas poisoning usually include tension, anxiety, jitteriness, restlessness, emotional lability, and giddiness. There may be insomnia and excessive dreaming, occasionally with nightmares. If the exposure is more marked, there follow headache, tremor, drowsiness, difficulty in concentrating, impairment of memory with slow recall of recent events, and slowing of reactions. In some persons there is apathy, withdrawal, and depression. With the appearance of moderate symptoms there occur abnormalities of the electroencephalogram, characterized by irregularities in rhythm, variation and increase in potential, and intermittent bursts of abnormally slow waves of elevated voltage similar to those seen in patients with epilepsy (Fig. 1). These abnormal waves become more marked after one or more minutes of hyperventilation, which, if prolonged, may occasionaly precipitate a generalized convulsion. If absorption of nerve gas has been sufficiently great the casualty then becomes confused and ataxic, and he may have changes in speech, consisting of slurring, difficulty in forming words, and multiple repetition of the last syllable. He may then become comatose. Reflexes may disappear, and respiration may become Cheyne-Stokes in character. Finally, generalized convulsions may ensue. With the appearance of severe central neural symptoms, depression of respiration, central in origin, may occur, adding to the respiratory embarrassment caused by weakness and airway obstruction. Depression of the circulatory center may also occur, resulting in a fall of blood pressure some time before death.

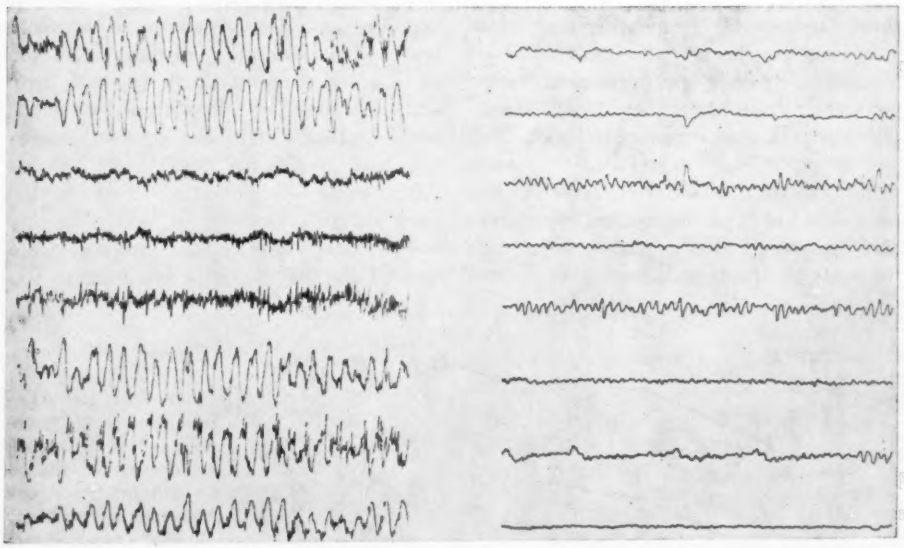

Fig. 1 (Case 3).—Effect of marked exposure to sarin on the electroencephalogram. Left, following exposure to sarin, showing high-voltage slow waves in temporofrontal and temporocentral leads. Right, two weeks later, showing return to normal. Bipolar leads: left prefrontal to left anterior temporal (top), left anterior temporal to left low central, left low central to left low occiput, left occiput to right occiput, right occiput to right low central, right low central to right anterior temporal, right anterior temporal to right prefrontal, right prefrontal to left prefrontal (bottom).

Effects of Nerve Gas Liquid

Local Effects.—The local ocular effects are similar to the effects of nerve gas vapor. If the concentration of nerve gas in the liquid reaching the eye is high, the effects will be instantaneous and marked,

and if the exposure of the two eyes is unequal the local manifestations will also be unequal. There is no immediate local pain or irritation. Following the ingestion of solutions containing nerve gas, the initial symptoms, which begin 20 to 30 minutes after ingestion, are usually gastointestinal. Nerve gas has no taste. Following cutaneous exposure there is no local irritant change, but sweating at and near the site of exposure and, at times, localized muscular twitching and fasiculation may occur. However, these may not be noticed, so that absorption through the skin may go undetected until systemic symptoms begin.

Systemic Effects.—These are similar to the effects of vapor, but the sequence and time course of symptoms vary with the route of exposure. Respiratory and ocular symptoms are the first to appear after inhalation of vapor; gastrointestinal symptoms after ingestion of liquid, and sweating after cutaneous exposure to liquid. Following comparable degrees of exposure, respiratory manifestations are severest after inhalation and gastrointestinal symptoms may be severest after ingestion. Otherwise the systemic manifestations are in general similar following exposure by any route, and the full-blown picture of severe nerve gas poisoning by any route is, in general, similar to that described following inhalation. However, marked miosis occurs only if there has been local exposure to liquid or vapor.

Time Course of Effects of Nerve Gas

Local effects appear within one to several minutes after exposure and may last for 1 to 14 days. The time course of the appearance of systemic effects varies with the degree and route of absorption. Following sufficient exposure to produce moderately severe systemic effects, the time interval to the onset of these effects is shortest after inhalation (several minutes), probably about the same after ocular exposure to liquid, and longer after ingestion or cutaneous exposure to liquid (one-fourth to two hours). The time interval between exposure and the occurrence of maximal severity of moderate symptoms is in the same order (approximately one-half, two, and six hours), as is the duration of symptoms (approximately one to five, two to five, and three to five days) Figs. 2 to 5). After lethal or near-lethal exposure, the time intervals to onset of symptoms and to maximal severity of symptoms are shorter and may be but a few minutes following overwhelming exposure. During the period of recovery symptoms may recur intermittently (Fig. 3), especially after exertion. After exposure to lethal concen-

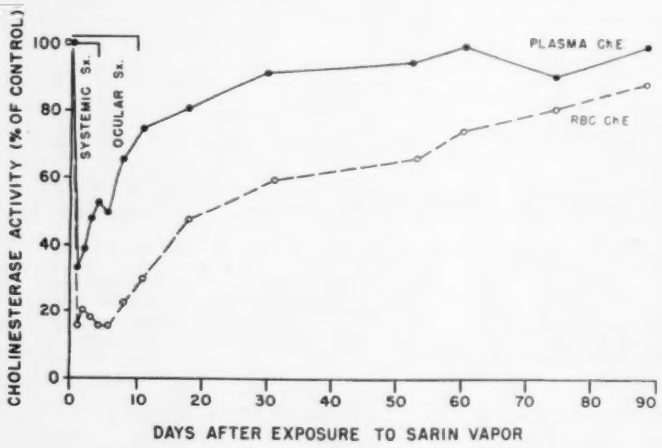

Fig. 2 (Case 1).—Time course of symptoms and of depression and restoration of plasma and red blood cell cholinesterase activity following exposure to sarin vapor. Cholinesterase activity [18] prior to exposure was 0.90Δ pH/hour (plasma) and 0.56 Δ p H/hour (red blood cells).

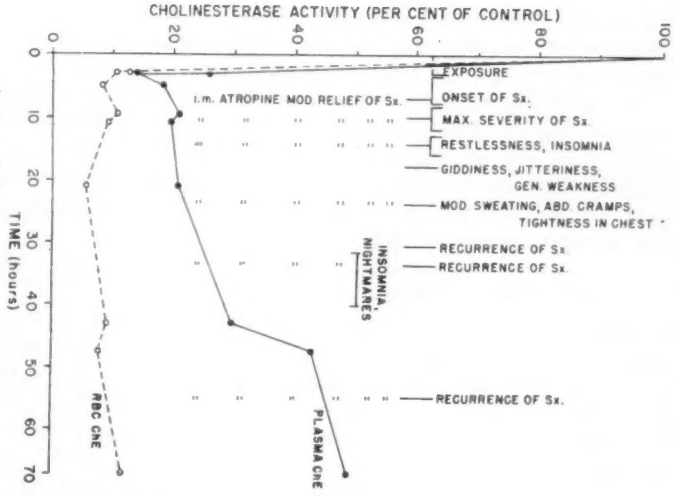

Fig. 3 (Case 2).—Time course of symptoms, atropine administration, and depression and restoration of plasma and red blood cell cholinesterase activity following percutaneous exposure to sarin liquid. Cholinesterase activity prior to exposure was 0.83ΔpH/hour (plasma) and 0.56 ΔpH/hour (red blood cells).

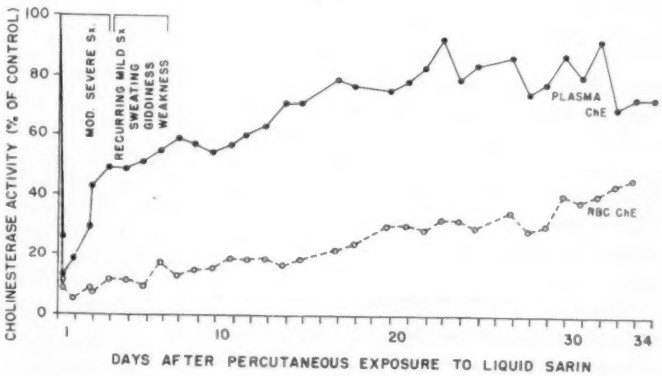

Fig. 4 (Case 2).—Further restoration of plasma and red blood cell cholinesterase activity following depression by percutaneous exposure to sarin.

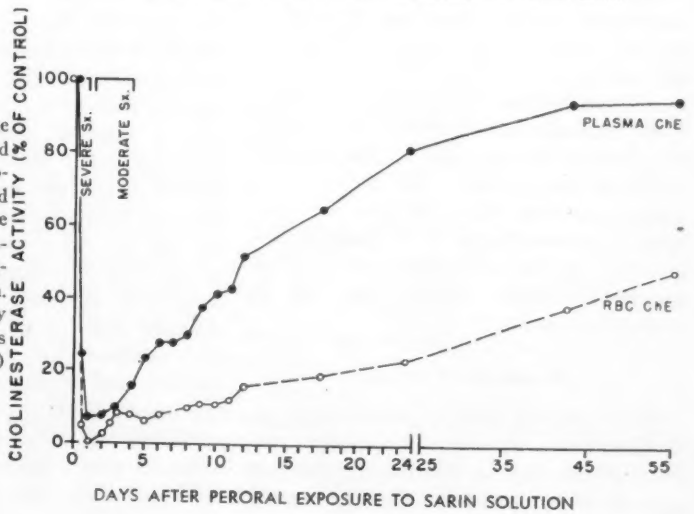

Fig. 5 Case 3).—Time course of symptoms and of depression and restoration of plasma and red blood cell cholinesterase activity following peroral exposure to an aqueous solution of sarin. Cholinesterase activity prior to exposure was 1.02 ΔpH/hour (plasma) blood cells).

trations the time interval to death depends upon the degree and route of exposure. After exposure to a concentration of vapor or of liquid that is just lethal, it is likely that, in the absence of treatment, death would usually occur within one to several hours, and following exposure to several times the lethal concentration, within several minutes to one-half hour.

Cumulative Effects of Repeated Exposure

Daily exposure to concentrations of nerve gas which are insufficient to produce symptoms following a single exposure may result in the onset of symptoms after several days. Continued daily exposure may be followed by increasingly severe effects. After symptoms subside, increased susceptibility persists for one to several days. The degree of exposure required to produce recurrence of symptoms and the severity of these symptoms depend on the extent of, and time interval since, the last exposure. Increased susceptibility is not limited to the particular nerve gas that was initially absorbed but applies to any of the nerve gases.

Cause of Death

Death is caused by respiratory failure resulting from weakness of the muscles of respiration, central depression of respiration, and airway obstruction by bronchial and salivary secretions and perhaps by bronchoconstriction. If respiration is maintained artificialy and secretions are removed by postural drainage and suction and diminished by atropine, the patient will usually survive, unless the exposure has been so overwhelming as to produce depression of the circulatory center, with peripheral vascular collapse and fall in blood pressure.

Postmortem Findings

Aside from the decrease in the activity of cholinesterase enzymes throughout the body, which may be detected by chemical methods or by special staining, the organic phosphate anticholinesterase compounds produce no specific lesions detectable by ordinary gross or histologic examination. At postmortem examination there may be capillary dilatation, hyperemia, edema of the lungs, and plugging of the smaller air passages, and there may be hyperemia and edema of the brain and other organs.

Diagnosis

Signs and Symptoms

Identification of nerve gas poisoning can be made from the characteristic signs and symptoms. If exposure to vapor has occurred, the pupils will be very small, usually pinpoint. If exposure has been cutaneous, or has followed ingestion, the pupils may be normal, or, in the presence of severe systemic symptoms, slightly to moderately reduced in size. In this event, the other manifestations of nerve-gas poisoning must be relied on to establish the diagnosis. No other chemical warfare agent produces pinpoint pupils (in the absence of severe conjunctival inflammation), muscular twitching and fasciculations, or the characteristic train of muscarine-like, nicotine-like, and central nervous system manifestations.

Effect of Atropine Administration

The administration of atropine alleviates the muscarine-like and central neural mainifestations of nerve-gas poisoning, even though, in severe poisoning, such relief may be transient and repeated administration of atropine may be required. The amount of atropine required to alleviate these manifestations varies with the severity of the poisoning, and the duration of the relief afforded by the atropine varies inversely with the severity of the poisoning. The administration of a single dose of 2 mg. of atropine by any route to a subject who has absorbed little or no nerve gas produces mild symptoms of atropinization in most subjects, and repetition of this dose within one or two hours produces more moderate symptoms of atropinization. In contrast, a subject who is having moderate manifestations of nerve gas poisoning will not de-

velop symptoms of atropinization after 2 mg. of atropine, and one who is having severe manifestations of nerve gas poisoning may not develop symptoms of atropinization even after the second dose of atropine.

Determination of Plasma and Red Blood Cell Cholinesterase Activity

The signs and symptoms produced by the nerve gases are due to inhibition of the cholinesterase enzymes of the nervous system, muscle, and secretory glands and not to the coincident inhibition of the cholinesterase enzymes of the plasma and red blood cells. However, the activity of the latter enzymes, which is most easily determined by electrometric measurement of change in hydrogen ion activity following hydrolysis of acetylcholine by plasma or lysed red blod cells,[18] may be used as a guide of some value in detecting systemic absorption of nerve gas and persistence of its effects. The determination is seldom essential when the clinical picture is clear, but it may be helpful, particularly in detecting subclinical exposure or mild poisoning or in determining cause of death. Local ocular and respiratory manifestations of nerve-gas poisoning may occur without any inhibition of plasma and red blood cell cholinesterase activity, but systemic manifestations are invariably accompanied by depression of the activity of these enzymes. The depression accompanying onset of systemic symptoms is less marked following rapid than following gradual absorption of nerve gas, presumably because rapid absplasma and red blood cell cholinesterases and more ready access of nerve gas to the cholinesterase enzymes of other tissues. The plasma and red blood cell cholinesterases at the time of onset of systemic symptoms due to a single exposure to sarin are depressed to approximately 60% and 50% of initial activity after inhalation of vapor, to 35% and 25% after ingestion of liquid, and to 15% and 10% after percutaneous exposure to liquid (Figs. 2 to 5).#

References 14-17.

Restoration of plasma cholinesterase activity begins 3 to 10 hours after cessation of exposure, and restoration of red blood cell cholinesterase activity, 24 to 48 hours after exposure. After marked depression, plasma cholinesterase returns to the original level of activity over a period of 30 to 40 days, and red blood cell cholinesterase, over a period of 80 to 100 days (Figs. 2 to 5). Repeated exposure to nerve gas at intervals of hours or days results in progressive depression of plasma and red blood cell cholinesterase activity, since there is insufficient time between exposures for restoration of activity to occur. Following repeated exposure there is no predictable correlation between the onset of symptoms and the precise level of cholinesterase activity of the plasma or red cells, except that this is depressed considerably below normal. The cholinesterase activity of the red blood cells may be gradually depressed to near zero by repeated exposures over a period of several days without systemic symptoms necessarily ensuing, or without any relation to the severity of the symptoms that occur. The red blood cell cholinesterase and, to a lesser extent, the plasma cholinesterase remain at a low level of activity long after the disappearance of symptoms.

In attempting to evaluate the significance of determinations of plasma and red blood cell cholinesterase activity, it must be kept in mind that the range of normal activity is fairly wide (1.0 ± 0.5 ΔpH/hour for plasma by the electrometric [18] method and 0.8 ± 0.4 ΔpH/hour for red blood cells). In addition, plasma cholinesterase activity may be moderately reduced by many acute or chronic illnesses, particularly those affecting liver function,* as well as following absorption of anticholinesterase compounds. On the other hand, red blood cell cholinesterase activity is reduced only by anticholinesterase compounds or by relatively uncommon blood diseases such as pernicious anemia or leukemia.†

* References 2-5.

† References 2-5.

Prevention of Poisoning and Handling of Casualties

The standard (U. S. Army, M-9A1) gas mask protects the respiratory tract and eyes against nerve-gas vapor, spray, or aerosol or nerve gas adsorbed on dust. Vapors of nerve gases in ordinary field concentrations are, in general, absorbed through the skin very slowly and to a minor degree, and so proper and prompt masking generally protects against the effects of vapor. Liquid nerve gas penetrates rapidly through ordinary clothing or impregnated permeable clothing, which offer very little protection to the skin against liquid splash. However, absorption through the skin occurs over a period of minutes, so that, unless the exposure is overwhelming, there should be sufficient time to remove contaminated clothing and blot and wash liquid nerve gas from the skin. Impermeable protective clothing, individual protective covers, and rubber gloves and aprons protect the skin against liquid nerve gas. Since the liquid, or solution, is more readily absorbed through abraded skin than through intact skin, breaks in the skin may be covered with adhesive tape prior to anticipated exposure. Absorption of the liquid through the conjunctivae is very rapid, and a drop of undiluted liquid may be lethal; consequently, protection of the eyes against splash and immediate washing away of ocular contamination are of the greatest importance.

Since absorption of nerve gas vapor by the respiratory tract is rapid, a gas mask must be put on immediately on signal, when the presence of vapor in the atmosphere is suspected or anticipated, or if any of the following signs and symptoms are noticed under conditions of potential exposure:

(1) A faint, sweetish, fruity odor, which cannot be accounted for

(2) Difficulty in breathing, either on drawing in a breath or on exhaling

(4) Small, pinpoint-sized pupils noticed in a mirror, or in the eyes of persons in the vicinity

(5) A drawing, slightly painful sensation felt in the eyes or unexplained dimness of vision, occurring in association with pinpoint pupils.

The breath should be held until the gas mask is on and properly adjusted. If the concentration of nerve gas in the atmosphere is high, the inhalation of a few breaths may result in sufficient absorption to be incapacitating, or even lethal. If the concentration in the atmosphere is not so high, a longer period of exposure may precede the onset of symptoms and the detection of poisoning. However, since the effects of nerve gas are progressive and cumulative, the prevention of further absorption is particularly urgent once symptoms have begun. For this same reason, casualties who are not wearing a gas mask must have this put on at once and properly adjusted. Gas masks should be worn until chemical test procedures indicate the absence of nerve gas in the air and the all-clear signal is given.

Casualties who have been contaminated with liquid nerve gas may endanger unprotected personnel, particularly since most of the nerve gases are volatile. Attendants should wear a gas mask and, if possible, protective heavy rubber gloves and aprons. When rubber gloves and aprons have been in contact with liquid nerve gas, they should be washed off with water as often as is practicable and changed for fresh equipment after several hours of continual use, since the liquid agent slowly penetrates even this protective equipment.[19] Ambulances and other vehicles used for the transportation of casualties contaminated with liquid nerve gas must have their interiors washed with water and aired before reuse whenever possible. If conditions permit, the aid station should be established up-wind from the most heavily contaminated areas. Casualties must be undressed in the open, and contaminated clothing, litters, blankets, and equipment left outdoors, down-wind from the aid station. Newly arrived gas casualties must be kept

separate from uncontaminated patients until contaminated clothing has been removed and liquid nerve gas washed from the skin. Casualties who have severe symptoms of nerve gas poisoning may present an alarming picture, with massive salivation, struggling for breath, cyanosis, twitching, contorted features, and convulsions. It is obvious that serious emotional reactions may occur among those observing these casualties and that measures must be taken to prevent or allay panic.

Liquid nerve gases, or solutions, can poison water and food and may render other supplies or equipment dangerous to handle without rubber gloves and gas mask. Water and food supplies that are suspected of recent contamination, or water from open sources in any area where a gas attack has occurred, should be examined for the presence of nerve gas by chemical test procedures prior to consumption. Water supplies should be decontaminated chemically if necessary. Contaminated food should be discarded, or the outer layers should be removed and the residue examined prior to use. Material contaminated with liquid nerve gas should be thoroughly washed with copious amounts of water by personnel wearing gas masks and, if possible, rubber gloves and aprons and rubber shoes or boots. Alkali will accelerate the destruction of liquid nerve gas; consequently, if it is feasible, material may be washed with as concentrated a solution of alkali as can be used without inflicting unnecessary damage. Nonessential supplies or equipment that are heavily contaminated with liquid nerve gas and which cannot be adequately washed or treated with alkali should be buried or burned.

Treatment Prior to Hospitalization

The immediate treatment of the nerve gas casualty consists of termination of the exposure, administration of atropine in adequate doses, removal of bronchial and salivary secretions, maintenance of a patent airway, and artificial respiration when needed.

Termination of Exposure

This is accomplished by promptly putting a gas mask on the casualty if the atmosphere is contaminated, removing contaminated clothing, washing away liquid skin contamination, and, after other treatment measures have been initiated, removing the casualty to an uncontaminated area. If a gas mask is not available, the casualty's face may be covered with a cloth saturated with water.

Liquid nerve gas must be promptly removed from the skin or clothing. Liquid on the skin should be blotted with a handkerchief, cloth, or piece of outer clothing. The blotting should be done without spreading the contamination and without rubbing the skin, which may increase contamination. A fresh cloth or piece of outer clothing should then be soaked with water and rubbed over the contaminated area firmly enough to remove any remaining liquid contamination, as well as dirt, but not so hard as to abrade the skin or produce reddening. The cloth should be turned over to expose clean wet cloth to the skin with each rubbing. The skin should be washed with copious amounts of water and with soap, if possible. Contaminated clothing should then be quickly removed or cut away, and discarded. When heavy contamination of a limb by nerve gas liquid has occurred, a tourniquet may be applied about the limb just proximal to the contaminated area in order to reduce systemic absorption. It should be tied tightly enough to occlude the pulse, loosened for about half a minute at 10-minute intervals over a period of 30 minutes, and then removed. If the tourniquet is allowed to remain in place continuously for more than 15 minutes there will be danger or nerve damage and of gangrene of the ends of fingers or toes, especially in older subjects. When the temperature is near or below freezing, use of the tourniquet to delay nerve gas absorption should be omitted.

If liquid nerve gas should get into the eye, instant action is necessary to prevent

absorption of a lethal dose. The head should be tilted back so that the eyes look straight upward, and water poured slowly into the contaminated eye, which is held open with the fingers. The water should be poured slowly, so that the irrigation will not last less than 30 seconds. This irrigation must be done in spite of the presence of nerve gas vapor. The breath should be held as much as possible during the procedure, and the gas mask put on as soon as the irrigation is completed. The pupil of the contaminated eye should be watched during the next minute. If it rapidly gets smaller, 2 mg. of atropine should be injected intramuscularly at once. If the pupil does not get smaller, the ocular contamination was not by nerve gas, and atropine is not needed.

If ingestion of nerve gas is known to have occurred, gastric lavage with water should be carried out, if possible.

Administration of Atropine

The appearance of any local or systemic signs or symptoms of nerve-gas poisoning calls for the immediate injection of atropine. This drug inhibits the action of acetylcholine at its many sites of action, other than the voluntary muscles. As a result, it has a moderate inhibitory effect on the muscarine-like and central neural effects of nerve gas, but no appreciable influence on muscular weakness and fasciculations. In patients with severely impaired breathing due to nerve gas poisoning, atropine administration facilitates respiratory exchange by suppressing bronchial and salivary secretion and bronchoconstriction, and perhaps by diminishing central depression of respiration, but it does not appreciably restore strength to the respiratory muscles. In such patients atropine is employed as an adjuvant to artificial respiration.

Rate of Action.—The action of 2 mg. of atropine sulfate or tartrate begins 1, 8, or 20 minutes after intravenous, intramuscular, or oral administration, and is maximal in 6, 35, or 50 minutes. The effects of the drug administered in the same dose by any of these routes are approximately the same once absorption has occurred.

Syrettes and Ampins.—For the parenteral administration of atropine in the field Syrettes and Ampins are available, containing 2 mg. of atropine tartrate or sulfate in solution (1.2 cc.). The Syrette is a tin or plastic tube, the contents of which are squeezed out after insertion of the attached needle intramuscularly or intravenously. The seal between the needle and tube is first punctured by the stylet that is in place within the needle. The Ampin is a glass ampule containing solution pressurized by helium gas at 2.5 atmospheres and connected to a needle by a short rubber tube. After insertion of the needle intramuscularly, the ampule is tilted so that its bottom points straight up, and the tip of the ampule in the rubber tube is crushed, alowing the compressed gas to force the liquid out.

Dose.—Atropine should be injected immediately after the appearance of any local or sytemic signs or symptoms of nerve gas poisoning. If appreciable absorption of nerve gas is known to have occurred, 2 mg. of atropine may be injected intramuscularly before the effects of poisoning appear, but it is best to avoid administration of atropine when absorption of nerve gas is merely suspected. In order to avoid the administration of incapacitating doses of atropine to persons who have absorved little or no nerve gas, self-administration of this drug should be limited to 2 mg. and administration by personnel other than physicians should be limited to a total of 6 mg.[20] Atropine should not be administered for preventive purposes prior to contemplated exposure to nerve gas, as this may increase absorption by the respiratotry tract as a result of inhibition of bronchial secretion and bronchoconstriction.

When signs or symptoms produced by nerve gas are mild, 2 mg. of atropine should be injected intramuscularly and re-

peated at 20-minute intervals until muscarine-like symptoms are relieved and signs of mild atropinization (dry mouth and skin) appear. A mild degree of atropinization should then be maintained for at least 24 hours by the intramuscular or oral administration of 1 or 2 mg. of atropine at intervals of one-half to four hours.

When symptoms of nerve gas poisoning are moderately severe, 2 to 4 mg. of atropine should be injected intravenously, or, if this is not feasible, intramuscularly, and repeated in doses of 2 mg. at 3- to 8-minute intervals until muscarine-like symptoms appear. The site of intramuscular injection may be massaged for several minutes to hasten absorption. A mild degree of atropinization should be maintained for at least 48 hours.

When severe symptoms are present, particularly respiratory distress or convulsions, 4 to 6 mg. of atropine should be injected intravenously, or, if this is not feasible, intramuscularly, and repeated in doses of 2 mg. at 3- to 8-minute intervals until bronchial secretions and salivation decrease and convulsions cease. In severe nerve-gas poisoning the effect of each injection of atropine may be transient, lasting only 10 to 30 minutes. Therefore the patient must be observed as closely as possible for recurrence of signs of poisoning and atropine must be repeated at appropriate intervals to relieve the muscarine-like and central neural effects of nerve gas and to maintain a mild degree of atropinization for at least 48 hours (Fig. 3). In severe poisoning as much as 24 to 48 mg. of atropine may be required the first day (Table 2).

Syptoms Produced by Atropine.—In the presence of systemic evidence of nerve-gas poisoning there is increased tolerance for atropine, so that fairly large doses may be administered before signs of atropinization appear. In severe nerve-gas poisoning as much as 24 to 48 mg. of atropine may be administered in a day without producing more than transient and mild symptoms attributable to atropine. The absence of increased tolerance for atropine would indicate that nerve-gas poisoning is probably either not present or is mild.

In subjects who have absorbed little or no nerve gas, the administration of a single dose of 2 mg. of atropine by any route produces mild symptoms of atropinization, including dryness of the mouth and pharynx, with slight difficulty in swallowing, subjective warmth, slight flushing, slight tachycardia, some hesitancy of urination, and occasional desire to eructate. The pupils may be slightly dilated, but they react to light. In some subjects there may be mild drowsiness, slowness of memory and recall, subjective slowing of motor activity, and blurring of near vision, particularly after the intravenous administration of atropine. Some subjects may have mild postural hypotension. These symptoms should not interfere with ordinary activity except in the occasional person who proves to be unusually reactive to the central neural effects of atropine and except in hot environments, where interference with

TABLE 2.—*Measures Required for the Treatment of Intoxication Due to Organic Phosphate Anticholinesterase Compounds (Sarin, Tetraethylpyrophosphate (TEPP), and Octamethylpyrophosphoramide (OMPA)*[a]

Case	Anticholinesterase Compound	Severity of Symptoms	Atropine Administered					
			Route	Total Dose, Mg.	Time of Administration, Hr.	Suction	Intubation	Artificial Respiration
2	Sarin	Moderately severe	i.m.	6.5	13	0	0	0
4	Sarin	Moderately severe	i.m.	16	48	0	0	0
5	Sarin	Moderately severe	i.v. & i.m.	15	28	0	0	0
3	Sarin	Very severe	i.v. & i.m.	21	39	+	0	+
6	TEPP	Very severe	i.v. & i.m.	24	24	+	+	+
7	OMPA	Very severe	i.v. & i.m.	50	24	+	+	+

[a] Atropine was administered in doses of 1 to 2 mg. as frequently as needed to alleviate the muscarine-like and central neural effects of the anticholinesterase compound.

sweating and elevation of body temperature may occur. If a second dose of 2 mg. of atropine is given within an hour, the symptoms become moderate in degree and most subjects will be drowsy and have some blurring of near vision, but almost all will be able to continue ordinary activity at reduced efficiency. A third dose of atropine administered within an hour will result in more marked symptoms, which will interfere with ordinary activity in many subjects but will usually not be totally incapacitating. Further administration of atropine at frequent intervals will result in severe and incapacitating symptoms of overatropinization, including very dry mouth, thirst, hoarseness, dry flushed skin, dilated pupils, blurring of near vision, tachycardia (up to 160 per minute), urinary retention, constipation, slowing of mental and physical activity, restlessness, headache, giddiness, disorientation, hallucinations, increasing drowsiness, and, sometimes, maniacal behavior. Abnormal behavior may require restraint. Body temperature may increase, particularly in a warm environment or after exercise. The effects of atropine are fairly prolonged, lasting 3 to 5 hours after one or two injections, 6 to 12 hours after four injections at close intervals, and 12 to 24 hours after marked overatropinization. Overatropinization may be incapacitating, but fortunately only extremely high doses endanger life. A single dose of 10 mg. of atropine has been inadvertantly administered intravenously to normal adults without endangering life, even in the absence of any prior absorption of nerve gas, although it has, of course, produced very marked signs of overdose.

Removal of Secretions and Maintenance of Patent Airway

If the casualty is having excessive bronchial secretion and salivation, he should be placed in the prone position with the head to one side, and the foot of the litter or bed should be elevated to promote drainage. If airway obstruction occurs, the collar should be loosened, the mandible elevated, the tongue pulled forward, and saliva and mucus cleared periodically from the mouth and pharynx with cloth-covered fingers and, if possible, by means of suction through a catheter introduced through the mouth or nose. An oropharyngeal or nasopharyngeal airway may then be inserted and suction carried out intermittently as needed through and around the airway, which will generally be tolerated only by unconscious or flaccid patients.

If the upper airway remains obstructed and adequate exchange of air does not occur in spite of good efforts to carry out artificial respiration, an endotracheal catheter may be inserted. This should be attempted only in a casualty who is cyanotic because of airway obstruction and who is also either unconscious or flaccid and therefore unable to struggle and resist efforts at intubation. While this measure is best performed in a field hospital, rapid progression of symptoms may require that it be carried out by a trained physician in the aid station. The subject is placed on his back, with the head lifted straight up until the shoulders are slightly elevated, and under direct vision a laryngoscope is passed down the dorsum of the tongue until the epiglottis is visualized. It is then passed under the epiglottis, which is lifted to visualize the vocal cords. The endotracheal tube, lubricated with water-soluble jelly, is inserted into the glottis with a rolling motion and gently passed into the larynx and trachea for a distance of about 3 in. A cuffed tube is preferable, as this prevents aspiration of secretions more completely than does an ordinary tube or a tracheotomy. When the tube is in place, a roll of gauze is inserted between the teeth to prevent the tube from being bitten as the patient recovers, and adhesive is tied about the endotracheal tube and gauze roll (separately) and taped to the face. Suction may then be carried out by means of a No. 16 catheter passed through the endotracheal tube. If air exchange through the endotra-

cheal tube is not evident, it should be removed and, if the airway is still obstructed, another attempt to pass it should be made. If the subject is able to struggle and resist passage of the endotracheal tube, attempts to pass it should be discontinued, as this procedure will be difficult and attempts to carry it out may result in injury and edema of the larynx. The endotracheal tube may be removed when the casualty regains consciousness and is breathing spontaneously.

Artificial Respiration

If respiration is severely impaired death may occur in a matter of minutes unless an effective method of artificial respiration is begun immediately and maintained continuously until spontaneous respiration is resumed. In severe casualties this may require several hours, necessitating one attendant for each casualty. In spite of the concomitant administration of atropine to reduce secretions and bronchoconstriction and careful attention to patency of the airway, increased airway resistance usually renders artificial respiration more difficult, requiring greater inspiratory pressure, than in respiratory failure due to most other causes. Fortunately, airway resistance may diminish following the initial inflation of the lungs, making subsequent exchange less difficult.[21] Care must be taken to avoid delivery of excessive inspiratory pressure against high airway resistance, as this favors movement of air into the esophagus and gastric dilatation.[21]

Manual artificial respiration may not produce adequate exchange in severe casualties who have increased airway resistance, but it may have to be employed if no other means are available. The Holger-Nielson method, which produces active inspiration, is preferable to the Shaefer prone pressure method, which depends solely on elastic recoil of the compressed chest for inspiratory pressure. In the former procedure, the casualty is placed in the prone position, face to one side, neck hyperextended, with hands under the head. The operator kneels at the casualty's head and grasps the arms just above the elbows. He lifts the casualty's arms upward and forward (toward the head), expanding the chest and causing active inspiration. He then releases the patient's arms, causing passive expiration. He then places his hands on the casualty's back near the lower borders of the scapulae and exerts pressure on the chest, resulting in active expiration. The pressure is then released, causing passive inspiration. This cycle is repeated 12 to 15 times per minute.

Hand-operated bellows provide sufficient inspiratory pressure to overcome airway resistance and are effective in maintaining exchange. When used in a contaminated area, the bellows must be provided with a canister at the intake valve and with an expiratory valve. The bellows-mask must be held firmly to the face and the mandible supported with one hand while the bellows is compressed with the other.

In mask-to-mask artificial respiration the attendant respires the casualty by means of a tube connecting the expiratory outlet of the former's gas mask to the inlet of the latter's mask, which is equipped with an outlet valve that may be opened to permit passive expiration.† This method has the advantages of leaving the attendant's hands free to support the casualty's jaw and mask and of permitting him more easily to evaluate airway obstruction and adequacy of exchange. The operator must double his normal ventilation to compensate for the lower oxygen and higher carbon dioxide content in expired air.[21] In a noncontaminated area the attendant's mask is not needed. If no equipment is available, direct mouth-to-mouth breathing may be performed in a noncontaminated area as an adjunct to, or substitute for, manual artificial respiration.

Treatment of Ocular Sypmtoms

Ocular symptoms produced by the local absorption of nerve gas do not respond to

† References 21 and 22.

the systemic administration of atropine, but they are relieved by the local instillation of 2% homatropine, or 1% atropine, repeated as needed at intervals of several hours for one to three days. If local ocular effects of nerve gas are present, the size of the pupil cannot be used as an indicator of the systemic effects of nerve gas or of atropine.

Treatment in the Hospital

The measures initiated prior to hospitalization may be continued and supplemented by the use of suction drainage of secretions from the mouth, nose, or endotracheal tube and the administration of oxygen. Artificial respiration may be continued by means of hand-operated bellows or breathing bag, mask-to-mask procedure, or by mechanical means, which allow a greater number of casualties to be cared for by each attendant.

Mechanical Artificial Respiration

This may be carried out by either the negative-pressure body respirator or the positive-pressure-cycled resuscitator. The body respirator has proved to be effective and has the advantage of permitting more efficient suction of secretions from the pharynx or endotracheal tube. The pressure-cycled resuscitator should have a higher pressure range of operation (+27 and −15 mm. of mercury) than is commonly employed, in order to permit adequate inspiratory pressure to overcome airway resistance.[21] It should also be equipped with a manually controlled override with which the inflating pressure can be temporarily increased to +35 mm. of mercury when necessary.[21]

Management of Convulsions

If convulsions occur, tonic and clonic spasm of the respiratory muscles and of the glottis may greatly increase the difficulties of arificial respiration (Case 3). While the seizures are diminished by large doses of atropine and are likely to be followed by flaccid paralysis, during which ventilation can be better performed, it is possible that they may be so severe and prolonged as to interfere seriously with respiration and threaten life. In this situation, an anticonvulsant or muscle-relaxant drug may be administered intravenously, but excessive doses must be avoided lest respiration be depressed. Facilities must be available for intubation and artificial respiration. Trimethadione (Tridione), which is administered in doses of 1 gm. every 15 minutes up to a maximum of 5 gm., has less depressant effect on respiration than the barbiturates. If trimethadione is not available or proves ineffective, thiopental sodium (in 2.5% solution) may be administered. Curare may be injected in doses of 40 units every five or more minutes up to a maximum of 200 units.

Relief of Apprehension

If the casualty is apprehensive, he may be given a barbiturate by mouth in doses sufficient to allay apprehension and to produce mild sedation but not sufficient to produce marked drowsiness. This may be achieved by 0.1 gm. of sodium pentobarbital by mouth, repeated in one half hour and then every six hours, if necessary. Morphine should not be administered, as it may depress respiration.

Prevention of Pulmonary Infection

In casualties who have had severe respiratory depression or increased bronchial secretion penicilin should be injected intramuscularly to prevent or treat pneumonia. The occurrence of atelectasis may necessitate tracheal and bronchial aspiration.

Prognosis

If exposure to many times the lethal dose of nerve gas has occurred, or if treatment has been too long delayed, death may occur in spite of efforts to save the patient. This emphasizes the importance of prompt masking and of prompt institution of treatment. If recovery from nerve-gas poisoning occurs, it will be complete, unless

anoxia or convulsions have been allowed to go unchecked for so long a time that irreversible central nervous system changes due to anoxemia have occurred. Persistent paralysis attributable to peripheral neuritis has not been observed after nerve-gas poisoning, though it has been reported to occur occasionally after poisoning by the related compounds, parathion and Mipafox.[23]

Illustrative Cases

CASE 1.—A 29-year-old man was accidentally exposed to sarin vapor when an ampule of liquid sarin he was holding broke. He immediately left the contaminated area, removed his protective methacrylate (Plexiglas) eye shield, butyl rubber gloves, and clothing, and approximately one minute after exposure was under the shower. Two minutes after exposure vision in his right eye became dim and blurred and objects took on a brown color. There was moderate aching in the eye and photophobia. Five minutes after exposure these symptoms appeared in the left eye. Both pupils were maximally constricted to less than 1 mm. and were nonreactive to light. The conjunctivae and nasal mucous membranes were moderately injected. Thirty minutes after exposure the patient began to have moderately severe rhinorrhea, excessive salivation, sweating, anorexia, nausea, malaise, hot and cold "grippe-like" sensations, weakness, easy fatigability, and intermittent abdominal cramps which recurred every 5 to 10 minutes and lasted 10 seconds. He was tense, irritable, and depressed. Two hours after exposure 2 mg. of atropine sulfate was injected intramuscularly. This was followed by reduction in the severity of the abdominal cramps and sweating, but the ocular symptoms and rhinorrhea were not affected. Two drops (about 0.1 cc.) of 1% atropine solution were then placed in each eye. This provided marked relief from the eye pain and dimness of vision for a period of four hours, following which these symptoms returned to their initial severity. During the night the patient had insomnia and was very restless. The following day the ocular symptoms, irritability and depression were undiminished in severity, but other symptoms were milder. The pupils were still constricted, but not maximally, measuring 1.5 mm., and they were slightly reactive to light. All symptoms diminished gradually, the systemic symptoms and rhinorrhea disappearing by the 4th day after exposure and the ocular symptoms and signs by the 10th day after exposure.

The plasma and red blood cell cholinesterases were markedly depressed, to approximately 30% and 15% of normal activity, following the exposure. Plasma cholinesterase gradually returned to normal activity over a period of eight weeks, and red blood cell cholinesterase, over a period of three months (Fig. 2).

CASE 2.—A 30-year old man who had been exposed percutaneously to liquid sarin developed moderate generalized sweating, with twitching and cramps in his calf and thigh muscles, within half an hour after exposure.[18] One hour later the sweating became more profuse and abdominal cramps and giddiness appeared. The blood pressure rose from 115/80 to 150/100 mm. of mercury. One milligram of atropine sulfate was injected intramuscularly, and thereafter the sweating and abdominal cramps subsided for about an hour. Four hours after exposure moderate nausea appeared. Sweating became more profuse. There was moderate generalized weakness and easy fatigue on the slightest exertion. There was moderate dyspnea, with a sensation of tightness in the chest and reduction in vital capacity by nearly 50%. However, there was no audible wheezing on auscultation. Loud borborygmi were heard continually over the abdomen, and there were moderately severe abdominal cramps, slight tenesmus, and generalized muscular fasciculations. Five hours after exposure these symptoms increased. The patient felt weak, giddy, drowsy, restless, and apprehensive and had difficulty speaking. His symptoms were at maximal severity five to nine hours after exposure. Five, six, seven, ten, and thirteen hours after exposure the patient was given 1 mg. of atropine sulfate intramuscularly. Following each injection there was moderate relief of the gastrointestinal symptoms and mild relief of the central neural symptoms for about an hour. There were no signs of atropinization except for mild transient dryness of the mouth after the last three injections. During the night there was insomnia, excessive dreaming, and nightmares. The symptoms gradually subsided, and 19 hours after exposure there was only mild weakness and easy fatigability. However, 21, 28, 31, and 52 hours and 4 and 5 days after exposure there was recurrence of symptoms, most of which were relieved after the intramuscular injection of atropine. After the fifth day no further symptoms occurred, and there were no residual effects.

At the time of onset of symptoms the plasma and red blood cell cholinesterases were depressed to 12% and 8% of normal activity (Fig. 3). Plasma cholinesterase activity gradually returned to normal during the next three weeks, and red blood cell cholinesterase, during three months (Fig. 4).

CASE 3.—A 38-year-old man who had been exposed perorally to an aqueous solution of sarin developed within 30 minutes nausea, vomiting, abdominal cramps, generalized sweating, paresthesias in the lower extremities, withdrawal, depression, and apathy.[37] Ten minutes later he became unresponsive. His eyes remained open and had a glassy stare. There was profuse sweating and salivation and accumulation of secretions in the pharynx. Respirations became slow and stertorous, suggestive of partial upper airway obstruction. Expiration was prolonged, lasting 10 to 15 seconds, and inspiration was brief, lasting about 1½ seconds. Five minutes after the patient became unresponsive there was a general increase in muscle tone, followed by intermittent tonic and clonic generalized convulsive movements. There were periods of apnea, during which cyanosis ensued and respiration had to be maintained manually. The patient was given 1 mg. of atropine sulfate intravenously, followed in a few minutes by an additional 2 mg. The convulsions gradually became less severe. Sweating and salivation diminished, but secretions continued to accumulate in the pharynx and had to be removed by suction. The airway remained open, however, and endotracheal intubation did not have to be performed. One and a half hours after the onset of symptoms, respirations became more regular and the patient gradually regained consciousness. The sensorium remained clouded and speech remained difficult for several hours. The administration of atropine was continued at intervals, a total of 5 mg. being administered intravenously and 4 mg. intramuscularly during six hours after the onset of symptoms, followed by 1 mg. intramuscularly every 3 hours for 36 hours. There were no signs of atropinization, except for transient mild dryness of the mouth following the last few injections. The patient continued to be moderately apathetic, drowsy, and depressed, and he had insomnia until the fourth day after exposure.

At the time of onset of symptoms the cholinesterase activity of the plasma was reduced to 8% of normal, while that of the red blood cells was 0. An electroencephalogram obtained after the onset of unconsciousness and before the onset of convulsions disclosed marked slowing, with bursts of high-voltage five-per-second waves in the temporofrontal leads (Fig. 1). Abnormalities in the electroencephalogram persisted for six days. After this, there were no residual effects except for depression of plasma and red blood cell cholinesterase activity, which gradually returned to normal over periods of four weeks and three months (Fig. 5).

Comment

The total doses of atropine that were required to ameliorate the muscarine-like and central neural symptoms in Cases 2 and 3 are recorded in Table 2. The amount required by two other patients who had been exposed to sarin and by two patients who had been exposed to related anticholinesterase compounds are also listed. In each instance only mild and transient signs of atropinization occurred, in spite of the large amount of atropine administered. In the three patients who had very severe symptoms there were respiratory depression and upper airway obstruction, which necessitated frequent suctioning, artificial respiration, and, in two of the patients, endotracheal intubation. In the latter patients respiration was maintained by a Drinker body respirator for 12 hours. All six patients recovered completely, without residual effects.

The manifestations and treatment of poisoning by nerve gas are very similar to those of other organic phosphate anticholinesterase compounds, including the insecticides parathion, tetraethylpyrophosphate (TEPP), and hexaethyltetraphosphate (HETP). The manifestations are entirely attributable to inhibition of cholinesterase enzymes in the tissues and accumulation of acetylcholine. Ocular and respiratory effects may follow purely local exposure. Systemic absorption results in accentuation of the respiratory effects, in other muscarine-like symptoms, and in nicotine-like and central neural manifestations. Measures for prevention of poisoning include prompt masking and removal of liquid contamination from skin and clothing. Treatment consists of the administration of large doses of atropine, alleviation of airway obstruction, and artificial respiration and oxygen when needed.

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Case Reports

ACUTE NONSPECIFIC IDIOPATHIC PERICARDITIS

Report of a Case Treated with Orally Administered Cortisone

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Introduction

THE LATE Dr. Henry A. Christian,[1] in a manuscript received for publication the day of his death, recalled that during his student days at John Hopkins Medical School in 1898 he read in Osler's "Principles and Practices of Medicine," second edition, published in 1895, of idiopathic or primary periocarditis and that the term idiopathic pericarditis appeared in the title of many papers dating back to 1854 in the first series of the "Index Catalog of the Surgeon General's Office," in Washington, D. C., in the volume published in 1889. In a lecture as Hersey Professor of the Theory and Practice of Physic at the Harvard Medical School in 1901 he said, "Now as far as pericarditis is concerned, you can get a primary pericarditis, primary in the sense that you have no other inflammatory process in the body, you have no particular portal of entry that you can demonstrate, and so far as you can see, the primary condition, the sole condition, is an inflammation of the pericardium. These cases are comparatively rare. Now you find in a good many text books (Osler, etc.) the term, idiopathic pericarditis, used. That simply means that it is an infection the cause of which is not known. In a certain number of these cases when they come to autopsy, if you make cultures from the pericardium, you find no bacteria."

Later medical literature is surprisingly scant in mention of this syndrome until 1942, when Barnes and Burchell,[2] in reporting 14 cases of acute benign nonsuppurative pericarditis simulating acute ischemic myocardial disease, stressed the diagnostic electrocardiographic alterations. Subsequent numerous authors* have garnished the clinical and laboratory features of this syndrome with a galaxy of designations and, in particular have emphasized the differential diagnosis from coronary artery thrombosis with myocardial infarction with its prognostic and therapeutic connotations.

Although the disease seems intimately related to an aseptic upper respiratory infection, the etiology has proved an enigma, but because the serosanguinous pericardial effusion is free from bacteria on routine smears, cultures, and guinea pig inoculation, a filterable viral origin has been postulated. The failure of conventional antimicrobial agents to beneficially affect the clinical course of the disease seems in keeping with the latter hypothesis.

Although the clinical course is purportedly benign and the mortality nil, frequently a prolonged devastating illness is associated with untoward profound toxic systemic manifestations. An agent which could mitigate the latter and control the morbidity without significant perverse reaction seems warranted a trial. Kursban and Iglauer[9] after 16 days of unsuccessful therapy with penicillin, chloramphenicol, chlortetracycline (Aureomycin), and salicylates noted a spectacular response with adrenocorticosteroid therapy (corticotropin) viz.: defervescence, dissipation of chest pain and pericardial friction rub, and diminution of cardiac silhouette within 48 hours. This advantageous effect might perhaps be considered fortuitous in a self-limited disease process. It therefore appeared worth while to report another se-

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* References 3-8.

vere case subjected to adrenocorticosteroid therapy.

Report of Case

A theater manager, 52 years of age, was referred to the Kingston Hospital Aug. 6, 1954, with a diagnosis of "coronary artery thrombosis." Thirty-six hours earlier, according to his statements, after profuse perspiration, attributed to the hot night, exposure to strong winds while he was walking home produced a "neuralgic" pain in the right neck and face somewhat alleviated by household analgesics. The following noon he experienced pain in right anterior chest aggravated by deep inspiration. During the evening exertional dyspnea with faintness ensued and the chest pain, now confined to the precordial area, progressively worsened and was intensified with even normal inspiration and trunk movements. The nonradiating precordial pain during the early hours of Aug. 6 became excruciating, necessitating massive parenteral opiates, and was accompanied by profound respiratory embarrassment. Singularly absent was a history of antecedent respiratory infection, cough,

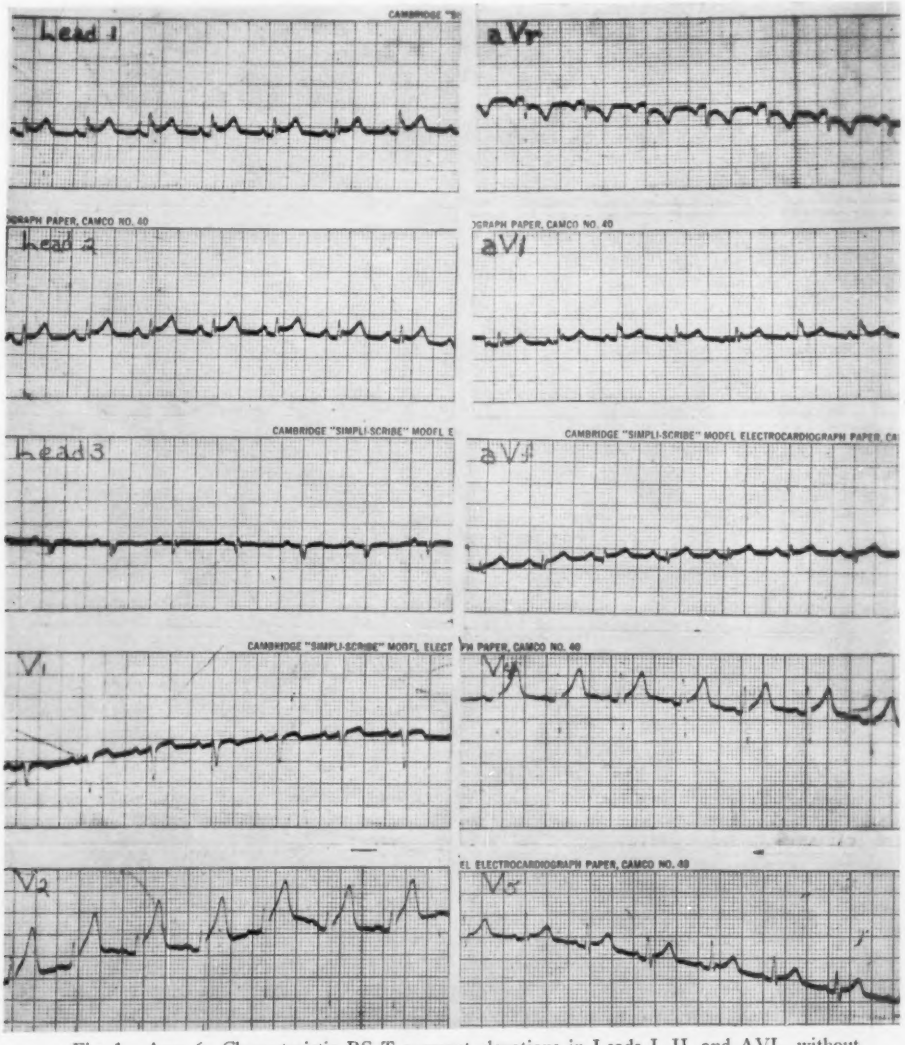

Fig. 1.—Aug. 6. Characteristic RS-T segment elevations in Leads I, II, and AVL, without reciprocal depressions in Leads III and aV_F but with depressed RS-T segment in Lead aV_R.

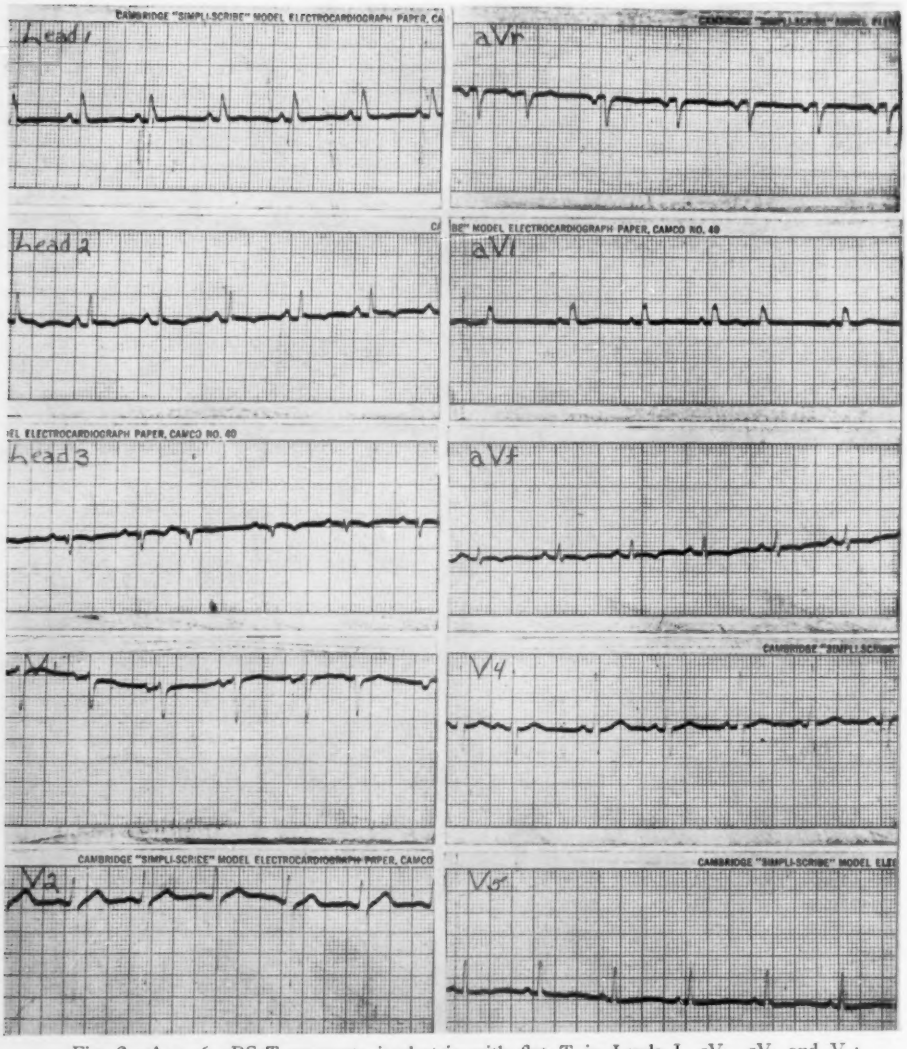

Fig. 2.—Aug. 6. RS-T segments isoelectric with flat T in Leads I, aV_r, aV_1 and V_5; inverted T in Leads II, III, and aV_f; absence of significant Q waves.

rigors, or peripheral circulatory collapse. The past history was free from evidence of cardiovascular or respiratory disease.

Routine examination revealed an acutely ill, prostrate, sthenic white man with moderate respiratory embarrassment complaining of severe constant nonradiating precordial pain. A blood pressure of 90/64-60 in the right arm was accompanied by tachycardia (120) without pulsus paradoxus. P_2 was greater than A_2, but no adventitious sounds were audible over the precordium and no cardiac enlargement was detected. Occasional bilateral basal coarse rales were not associated with detectable pleuritis. Retinopathy, clubbing of fingers, distended neck veins, and hepatomegaly were absent. Moderate pyrexia (of 102.2F) was associated with leucocytosis (WBC 22,000) with 90% granulocytes, and an erythrocyte sedimentation rate (Cutler) of 5 mm. in 60 minutes. Urine and serological studies were not informative. A teleoroentgenogram disclosed enlargement of the cardiac silhouette, and specific electrocardiographic alterations inspired

the diagnosis of acute nonspecific pericarditis, despite absence of pericardial rub.

The precordial pain, patently aggravated by trunk movements and inspiration, proved refractory to parenteral opiates; the pyrexia and sinus tachycardia persisted despite massive parenteral penicillin, and respiratory embarrassment necessitated oxygen. On Aug. 8 pleuritic pain in the left axilla was noted, followed 24 hours later by initial detection of a loud diffuse pericardial friction rub accompanied by pulsus paradoxus, and the roentgenographic cardiac silhouette was suggestive of pericardial effusion. A pericardiocentesis by Dr. Joseph Jacobson, thoracic surgeon at Kingston Hospital, yielded 50 cc. of a serosanguinous fluid with an occasional erythrocyte, free from organisms on direct smear, sterile after prolonged incubation, and free from evidence of tuberculosis on guinea pig inoculation.

With the appearance of pericardial friction rub the precordial pain abated, and only slight fever continued (temperature of 100.0 to 101.0 F); leucocytosis diminished (WBC 13,400, with 70% granulocytes). Episodes of profuse diaphoresis no longer occurred, and on Aug. 13 removal from the oxygen tent was not attended by recurrence of precordial pain or respiratory embarrassment, but pulsus paradoxus and pericardial rub persisted

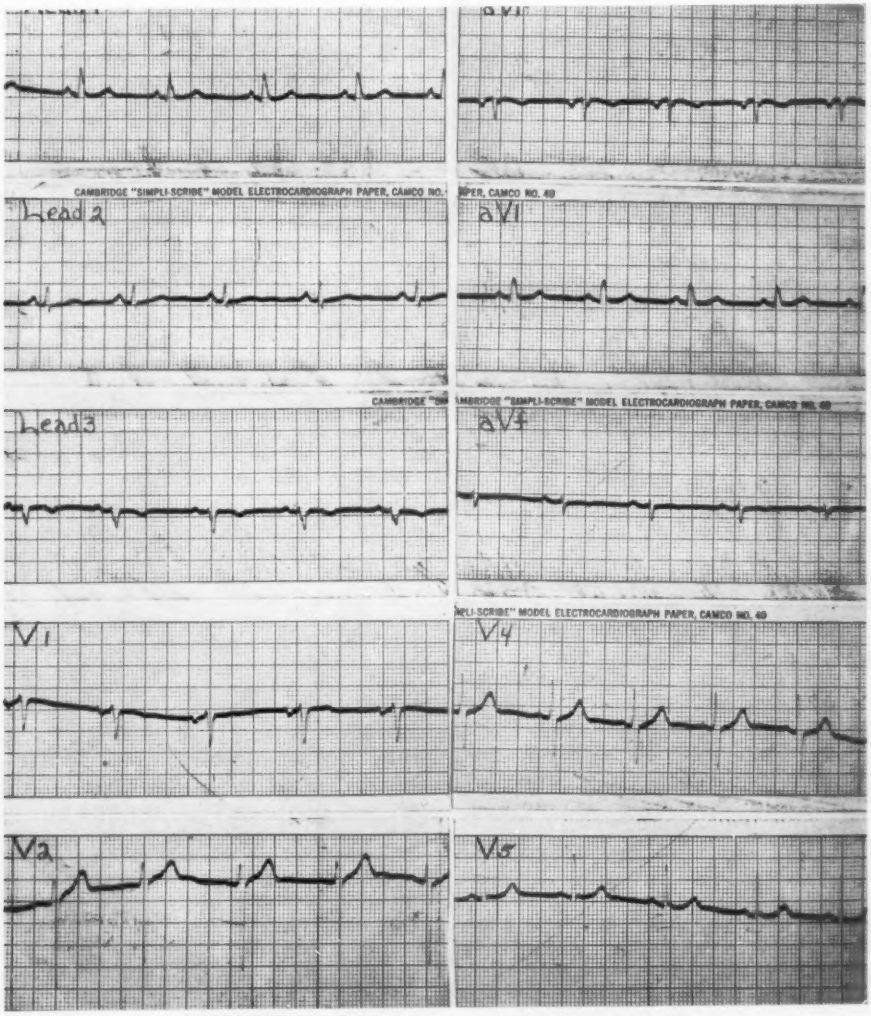

Fig. 3.—Oct. 1. Electrocardiogram within normal limits.

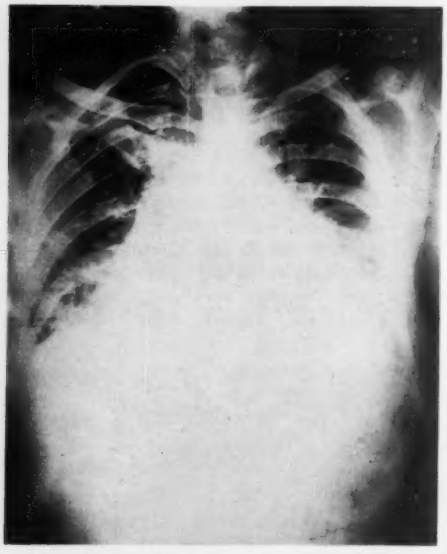

Fig. 4.—Aug. 11. Teleoroentgenogram demonstrating pronounced enlargement of cardiac silhouette.

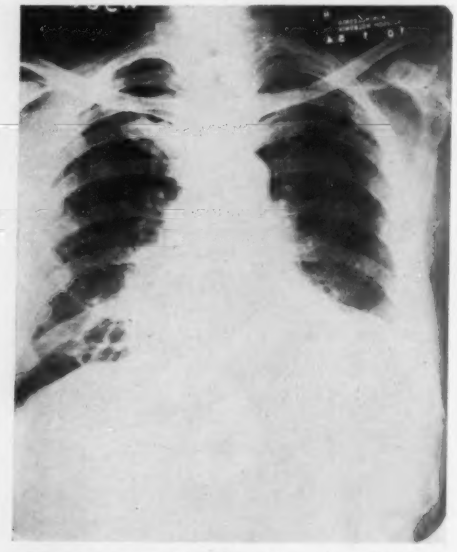

Fig. 5.—Sept. 12. Normal cardiac silhouette with residual left pleuritis obliterating the left costophrenic angle.

without significant neck vein distention, and electrocardiograms revealed less RS-T segment elevation. Subsequently, despite massive penicillin and streptomycin therapy, low-grade fever continued, with only slight diminution in the pericardial friction rub, but the tachycardia abated and sense of well-being returned. On Aug. 16 electrocardiograms disclosed isoelectric RS-T segments with inverted T_3 and T_2; the leucocytes numbered 12,900 per cu. mm., with 71% granulocytes, and repeated blood cultures were sterile.

On Aug. 17, notwithstanding empiric antibiotic therapy, the clinical status abruptly deteriorated. A fever (temperature of 103.8 F) was attended by profuse diaphoresis, return of severe precordial pain magnified by inspiration, intensified pericardial rub, and granulocytic leucocytosis. Paradoxical pulse persisted; prostration followed, and respiratory embarrassment again necessitated oxygen therapy. Tetracycline (Achromycin) wistfully replaced penicillin therapy but to no avail.

On Aug. 19 the grave clinical picture still persisted, and now cortisone, 50 mg. every six hours, enhanced the therapy in a desperate search for succor. Within 18 hours spectacular clinical improvement ensued, with defervescence, loss of chest pain, pronounced diminution in pericardial rub, and restoration of sense of well-being. On Aug. 22 the patient was afebrile and asymptomatic, with only a barely audible localized pericardial friction rub, under cortisone, tetracycline, and streptomycin therapy. His clinical course continued uneventfully, with successive elimination of streptomycin and tetracycline, but a barely audible pericardial friction rub with pleural quality persisted, and skiagrams of the chest disclosed a left lower pleuritic reaction. On Aug. 28 the patient was afebrile and asymptomatic and ambulant about the room, with only an ephemeral faint pericardial rub, and the cortisone was gradually diminished in dosage until on Sept. 5 the daily dosage was only 25 mg. On this day fever and pericardial rub were absent, but moderate granulocytic leucocytosis with slight eosinophilia and increased rate of sedimentation persisted.

Surprisingly enough, within 24 hours prostration, pyrevia, severe precordial pain, loud pericardial rub, sinus tachycardia, and profuse diaphoresis recurred. Now cortisone exclusively, 100 mg. per day in divided doses, unencumbered by other drugs, effected a dramatic clinical improvement, and in 24 hours defervescence occurred, associated with loss of chest pain, disappearance of pericardial friction rub, and return of sense of well-being. Over a period of one week cortisone dosage was gradually diminished, and the patient was discharged home ambulant on Sept. 12, 1954, afebrile and asymptomatic, receiving cortisone, 10 mg. twice a day. The latter therapy was discontinued after two weeks, and thereafter he has been under observation for one year without recurrence of any symptoms, and electrocardiograms together with the cardiac silhouette have maintained a normal pattern.

Comment

The above case fulfills the criteria established by Barnes and Burchell, viz.: early almost simultaneous onset of characteristic pain, fever, and leucocytosis with prolonged pericardial rub; electrocardiographic pathognomonic evolutionary patterns; cardiac enlargement with sterile pericardial effusion and pleuritis, and tendency to relapse. The nature of the enlarged cardiac silhouette is controversial. The small amount of fluid obtained upon pericardiocentesis apparently belies the effusion per se as the sole factor, and the tenacious tachycardia with decided respiratary embarrassment is presumably congruous with cardiac dilatation.

The benignity of the disease has been prominently mentioned, but yet incapacitation may be drastically lengthy, and one fatality, attributed to unfortunate bishydroxyconmarin (Dicumarol) anticoagulant therapy, has been recorded.[10] Because the disease is purportedly self-limited and the clinical course favorable, only symptomatic therapeutic measures are usually utilized. However, in the above-described acutely ill patient with profound toxic constitutional reaction and potentially prolonged morbidity more vigorous therapy appeared justified. With few exceptions nonbacterial infections are refractory to drug therapy, including antimicrobial agents.[11] A filterable viral etiology for acute nonspecific primary pericarditis has been postulated and is consistent with current laboratory data. This type of pericarditis has proved unresponsive to not only empiric antimicrobial measures [12] but salicylates as well.

Theoretically, in such a nonspecific disease process corticosteroids would suppress the sterile local inflammatory reaction, mitigate the toxic systemic symptoms, and preclude fibrogenetic pericarditic sequellae (although no instances of the latter have been reported). Adversely, such therapy inhibits specific antibody response, but this apparently plays a minor role in the sterile inflammations. Furthermore, short-term oral cortisone therapy would obviate latent hazards by ease of control because of promptness and briefness of activity.[13]

In this case distressing pain, respiratory embarrassment, and toxic symptoms were speedily ameliorated by short-term oral cortisone therapy, and, additionally, the pericardial friction rub vanished. A conclusive opinion of such therapy on the basis of a single case is not contemplated, and the paucity of available material renders critical evaluation impossible.

Summary

Beneficial response to short-term oral cortisone therapy in a case of acute nonspecific idiopathic pericarditis is reported, with the hope that others will explore its possibilities.

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SPLENIC INFARCTION IN A PATIENT WITH SICKLE-CELL-HEMOGLOBIN-C DISEASE

Report of a Case Occurring Following Air Travel

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and
FRANK W. FURTH, M.D., Rochester, N. Y.

SULLIVAN,[1] in 1950, reported the occurrence of splenic infarction after air travel in a Negro whose erythrocytes exhibited the sickling phenomenon. Since 1950 a number of cases of splenic infarction in association with air travel in sicklemics have been reported.* By means of electrophoretic studies of the hemoglobin, it has been established that this type of infarction may occur in Negroes having either sickle-cell trait or sickle-cell-hemoglobin-C disease.[5] From previous reports, it appears that exposure to altitudes above 10,000 feet is required for splenic infarction to occur in persons with sickle-cell trait but that splenic infarction can occur in association with sickle-cell-hemoglobin-C disease upon exposure to altitudes abve 5000 feet.† All of the previously reported cases have been males, principally men in military service. The case reported here is that of a young Negro woman with sickle-cell-hemoglobin-C disease who developed splenic infarction during a commercial air flight.

Report of Case

A 19-year-old Negro woman was admitted to the Strong Memorial-Rochester Municipal Hospital, June 4, 1953, complaining of pain in the left flank and the left upper quadrant of the abdomen. The pain was intensified by inspiration. These symptoms had started approximately 36 hours earlier, during an air flight from California to Rochester, N. Y., and had been preceded by abrupt onset of nausea and vomiting shortly after the plane had left the ground.

There was no history of recurrent joint or abdominal pain, leg ulcers, or heart disease. However, she had had two previous admissions to this hospital in January and February, 1952, for gross painless hematuria. Physical examination in 1952 was within normal limits except for splenomegaly. The bleeding was found to be coming from the left ureter. Intensive study including cystoscopy, pyelography, and cultures failed to disclose the cause. The hematocrit value was 28%, and the blood smear showed numerous target cells, anisocytosis, hypochromia, and moderate poikilocytosis. A sickle-cell test was positive. Bleeding was controlled by the instillation of silver nitrate into the left renal pelvis. The patient's mother was found to have a positive sickling test but was not anemic. The father and four siblings were not available for study.

In March, 1952, the patient moved to California. She was in good health and had a normal pregnancy with an uncomplicated delivery while there. It was upon return to Rochester by air that the present illness began.

Physical examination now showed an acutely ill Negro woman with a temperature of 39.5 C, a pulse rate of 120, respiration rate of 20, and a blood pressure of 130/80. Pertinent findings were a pleuropericardial friction rub along the left sternal border extending to the axilla and splinting of the left chest, with dullness and decreased fremitus at the left lung base without rales. There was splinting and tenderness of the left upper quadrant of the abdomen. The spleen was felt 4 cm. below the left costal margin.

The hematocrit value was 28%; hemoglobin, 9.6 gm/100 ml.; reticulocyte count, 7.1%; white blood cell count, 26,000, and a positive sickling test was obtained with metabisulfite. The blood smear showed numerous target cells. The urine contained 4.3 Uhrlich units of urobilinogen in a two-hour specimen but no bilirubin. A chest x-ray showed elevation of the left diaphragm. Steady improvement followed the administration of sedatives,

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This study was aided by the Karl R. Schnepel Fund.

* References 2-7.

† References 2-7.

analgesics, parenteral fluids, and penicillin.

She was discharged June 13, 1953, in apparent good health but was readmitted two days later complaining of pain in the left upper quadrant of the abdomen, left lower chest, and left flank, with radiation to the left shoulder. She was acutely ill and had a temperature of 38.4 C. Examination again showed splinting of the left chest, with decreased breath sounds and dullness at the left lung base posteriorly. The degree of splenomegaly was unchanged. The hematocrit value was 31%; hemoglobin, 9.2 gm/100 ml., and the white blood cell count, 30,000, with a differential count of 85% neutrophiles, 10% lymphocytes, and 5% monocytes. The reticulocyte count was 7.4, and the icterus index was 7.5 and subsequently rose to 12. Urine urobilinogen ranged from 6.7 to 3.7 Ehrlich units per two-hour specimen. Serum protein fractionation with cationic detergents showed a total protein of 8.0 gm/100 ml., with albumin 3.0 gm., globulin 5.0 gm., α_1- and α_2-globulin 1.95 gm., β- and γ-globulin 3.05 gm., and fibrinogen 1.15 gm.[8] The direct Coombs antiglobulin test was negative.

On the third day she developed pain in the right chest and x-ray showed elevated diaphragm and fluid bilaterally, with an infiltrative density in the right costophrenic angle which had not been present previously. She was given a transfusion of 500 ml. of sedimented red blood cells, after which the hematocrit value rose to 40%. She slowly improved, and the temperature became normal on the 10th hospital day. At this time she developed arthralgia of the knees and elbows bilaterally. On the 11th hospital day hemoglobinuria without hematuria was noted and the serum was found to contain methamalbumin. The hemoglobinuria cleared in about 48 hours. The arthralgia slowly subsided, and chest x-rays showed gradual resolution of the pulmonary infiltration and pleural effusion. She was discharged July 9, 1953, on the 25th hospital day.

She has since remained in excellent health. At the time of this report (September, 1955) the spleen is not palpable at the left costal margin. The hematocrit value has remained between 36% and 38%. The serum proteins are normal, with albumin 5.4 gm/100 ml., globulin 2.6 gm/100 ml., and normal values for the globulin fractions and for fibrinogen.

A study of this patient's hemoglobin by paper electrophoresis showed the combination of hemoglobin S and hemoglobin C.[9]

Comment

It is established that splenic infarction can occur in Negroes with either sickle-cell trait or sickle-cell-hemoglobin-C disease upon exposure to the altitudes attained by aircraft.‡ Splenic infarction in these persons appears to be initiated by the lowered oxygen tension. With an adequate oxygen supply intravascular sickling does not occur in persons with sickle-cell trait [10] nor, in all probability, in those with sickle-cell-hemoglobin-C disease. As the alveolar oxygen tension decreases with increasing altitude and hypoxia develops, intravascular sickling takes place.§ Blood visocsity is incerased by the presence of sickled erythrocytes.[13] In the spleen, where sickle cells are selectively sequestered,[14] the rate of flow of the oxygen-deficient blood is slowed to a point where oxygen deprivation of splenic tissue occurs and causes necrosis.

The level of alveolar oxygen tension required to initiate splenic infarction in persons with sickle-cell trait is lower than that necessary to produce splenic infarction in persons with sickle-cell-hemoglobin-C disease.[5] Therefore, as occurred in the patient reported here, splenic infarction in persons with sickle-cell-hemoglobin-C disease can occur at or below the maximum equivalent altitude (8000 ft.) of commercial aircraft.[15] Splenic infarction apparently does not occur in a person with sickle-cell trait unless he ascends to an altitude of more than 10,000 ft. without supplemental oxygen.

Splenic infarction in association with air travel in Negroes with sickle-cell anemia has not been reported. The spleen of the adult with sickle-cell anemia is usually very small and atrophic. This seems to offer an explanation for the lack of splenic infarction with air travel in association with sickle-cell anemia. It might be expected that splenic infarction could be precipitated in a child with splenomegaly and sickle-cell anemia.

The incidence of the syndrome of splenic infarction among sicklemics is difficult to determine. It has been estimated that there are 18,000 to 20,000 Negroes with sickle-cell-hemoglobin-C disease in the United States.[16] To date, seven cases including the one reported here, of associated splenic in-

‡ References 2-7.

§ References 11 and 12.

farction, air travel, and sickle-cell-hemoglobin-C disease have been described. Although the incidence of this phenomenon is low, it points to the importance of accurately differentiating the variants associated with the sickling phenomenon so that those patients with sickle-cell-hemoglobin-C disease can be cautioned concerning the danger of air travel.

Hematuria occurred in the patient reported above and has been reported previously in association with sickle-cell anemia and trait and with sickle-cell-hemoglobin-C disease.[17] The pathogenesis of the hematuria has not been established, but in most instances it does not appear to be related to renal infarction.

Summary

Splenic infarction can be a consequence of air travel in persons with sickle-cell trait or sickle-cell-hemoglobin-C disease. A case of splenic infarction occurring in association with commercial air travel in a young Negro woman with sickle-cell-hemoglobin-C disease is reported. The pathogenesis of the infarction appears related to he hypoxia at increased altitude with consequent intravascular sickling and interference with splenic circulation. Since commerical air travel may present a hazard to patients with sickle-cell-hemoglobin-C disease, it is advisable to differentiate the genetic variants of sickle-cell disease by means of electrophoresis of hemoglobin and caution those persons with sickle-cell-hemoglobin-C disease about air-travel.

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Books

Edited By WILLIAM B. BEAN, M.D.

Book Reviews

Diagnostic Advances in Gastrointestinal Roentgenology: Selective Methods, with Clinical Evaluation. By Arthur J. Benrick, M.D. Pp. 131. Price $6.00. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

This is a small book and a relatively inexpensive one. It was reexamined with considerable care after a cursory reading had failed to disclose a reason to say anything more complimentary about it than just that.

To begin with, the title proves to be misleading. "Diagnostic Advances" would lead one to anticipate finding evidence of advanced thinking or accomplishment which had taken place in the field of gastroenterologic roentgenology within relatively recent years. One looks in vain for evidence that could be so described. In his preface the author states that the book is not intended for beginners but for those so situated that they cannot keep up with new techniques and with "more modern interpretations." Those who will find much novelty in this work have been far removed indeed from the literature and practice of the gastroenterologic roentgenology of the last 15 years or more.

This is not the place for a detailed account or enumeration of poorly contrived statements, illogical pronouncements, and frank inconsistencies. The book is clogged with them. It is also poorly edited, carelessly proofread, and badly organized in its texual matter.

All this is no reflection on the author's competence as a practical roentgenologic diagnostician or on the adequacy, even excellence, of his approach to diagnostic gastroenterology. Undoubtedly, he could have written a superb treatise on this subject had he chosen to weigh the effect of his words and sentences more carefully, to have become more familiar than he apparently is with what has been going on in this field all around him these many years, and to have chosen an editor and proofreader competent enough to have at least recognized the correct spelling of proper names and to check the correctness of the titles of the very meager bibliography.

A beginner in gastroenterologic roentgenology might derive considerable profit from a careful reading of this book, but he shold be warned to devote most of his attention to the factual representations about equipment and procedure and to exercise care before accepting many of the judgments and generalizations the author proffers. The reasonably well-informed reader, especially one who is also competent in this field, will find much in the book to be annoyed about.

HARRY M. WEBER, M.D.

Dermatologie der Mundhoehle und der Mundumgebung: Systematik, Morphologie und Grundzuege der Behandlung. By Priv.-Doz. Dr. Aloys Greither. Price, $9.45. Pp. 262, with 191 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1955.

The author of this short German monograph (262 pages) has recorded a great many facts and clinical observations on "Dermatology of the Oral Cavity and Adjacent Areas."

Although the subject matter is necessarily brief, each subject is comprehensively covered. In the 15 chapters on diseases of the mouth he discusses the anatomy and physiology; malformations and aberrations; specific and nonspecific infections; viral and mycotic infections; exanthems, bullous, eczematous, and other dermatological diseases; connective tissue diseases; metabolic and pigmentary diseases, and benign and malignant tumors. The final chapter discusses the relationship of diseases of the oral cavity acting as a mirror of systemic disease.

In spite of its conciseness, this book should prove helpful to the medical student, general practitioner, or any specialist who desires a knowledge of the oral cavity.

SAMUEL M. BLUEFARB, M.D.

Surgery in World War II: Vascular Surgery. Edited by Daniel C. Elkin, M.D. and Michael E. DeBakey, M.D. Price, $4.25. Pp. 465, with 54 illustrations and 88 charts and tables. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., 1955.

This work consists of compilation of the clinical experience gained by the United States Army Medical Department at three Zone of the Interior Vascular Centers in the management of vascular injuries and disease during and following World War II. A major portion of the text concerns the surgical treatment of 2471 arterial injuries, of which there were 593 arteriovenous fistulae and 221 traumatic arterial aneurysms. This surgical experience is concisely presented and well illustrated by numerous case reports and illustrations. With but few exceptions, the patients were treated surgically in an era which preceded the use of arterial homotransplants. A remarkably low morbidity and mortality are recorded.

Portions of the text dealing with the emergency management of patients whose injuries include serious vascular trauma will be found especially valuable to those interested in traumatic surgery and civilian defense preparations. In addition, an extensive experience with nontraumatic vascular disorders is presented in detail. The book is organized and printed in an easily readable manner which resembles closely that of current medical and surgical periodicals.

RODMAN E. TABU, M.D.

Topley and Wilson's Principles of Bacteriology and Immunity. By G. S. Wilson, M.D., F.R.C.P., D.P.H., and A. A. Miles, CBE., M.A., M.D., F.R.C.P. Price, $24.50. Pp.: Vol. 1, 1106; Vol. 2, 1224. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

The "gospel" according to Topley and Wilson has returned—refreshed, renewed, and sparkling. All bacteriologists and virologists should have a copy of "Topley and Wilson," and most do. All that has been wrong with it recently has been the need for a new edition. Here it is, and it is vastly impressive. To suggest that two men could survey such a great field of knowledge and "grasp at the fragment of truth" in the recent prodigious flow of scientific papers sounds almost impossible. This new edition proves this supposition wrong. It is divided into four parts: general bacteriology, systematic bacteriology, infection and resistance, and the application of bacteriology to medicine and hygiene. It is interesting to see that the sections which have been expanded from the previous edition are those which deal with antigen-antibody reactions, variation and inheritance in bacteria, bacteriophage, Brucella, anaphylaxis hypersensitiveness and allergy, host factors, and generalized and neurological virus diseases.

One can carp at the title, as this work deals not only with principles but also with the applications of both bacteriology and virology. It might be said that this is textbook of infectious disease. It is no longer only a textbook for undergraduate students but is a mine of information for postgraduate students in all fields. There are fascinating chapters here. The normal flora of the human body, herd infection and herd immunity, and the mechanisms of bacterial infection are some of them. I've used the book so much already that the binding has given way—maybe the binding should be stronger, as Topley and Wilson belongs on the laboratory bench and the office desk for constant reference. (The paper of the new edition is better than that of the last, and the print is clearer.) The production of these two volumes is otherwise excellent, and they are a pleasure to read.

Of course I haven't yet read all the 2330 pages, but those I have, in my own field, are well balanced and complete. It is a pleasure to recognize the Staphylococcus in place of the Micrococcus—and many other old friends.

The British school of Bacteriology and Virology can be proud of this contribution by the Director of the Public Health Laboratory Service (Dr. Wilson) and the Director of the Lister Institute (Dr. Miles).

So many people have used this text in the past with so much benefit that the sales of this new edition are assured. These two volumes can be recommended without reservation for all microbiologists, all internists dealing with infectious disease, and any practitioner of medicine who wants to get more out of the bacteriology he deals with daily.

J. MACLEAN SMITH, M.D.

Lectures on the Scientific Basis of Medicine: Vol III, 1953-1954. By various authors, under the auspices of the British Postgraduate Medical Federation. Price, $6.00. Pp. 398, with illustrations. University of London, The Athlone Press, 2 Gower St., London, W.C. 1, 1955.

The stated aim of this annual series of "Lectures on the Scientific Basis of Medicine," which are given under the auspices of British Postgraduate Medical Federation, is to present "an integrated continuously developing survey of current scientific research and its relation to clinical medicine and surgery." The list of authors is a selective review of active British scientists, investigators, and clinicians. This is the kind of book which is helpful not only for

teachers and those in academic medicine and research but also could go a long way toward keeping the physician in practice abreast of the newer developments. This volume maintains the high level of excellence of its predecessors by continuing to supply illuminating comment on regions of medical advance where active research goes on. The scope is broader than that of the "annual review" or "yearbook" series. Since the references have included a large number of British and some continental work, it is particularly important for those whose reading is largely confined or wholly restricted to medical writings in the United States. Unhappily, the value of the references is reduced substantially by omission of the titles of most of the articles. The value of the book as a reference manual is lost by the absence of the index. It must be read through or used as a text. This, of course, is its purpose.

WILLIAM B. BEAN, M.D.

Books Received

1956 Medical Progress: A Review of Medical Advances During 1955. Edited by Morris Fishbein, M.D. Price, $5.50. Pp 399. McGraw-Hill Book Company, Inc., 330 W. 42d St. New York 36, 1956.

Gestation: Transactions of the Second Conference March 8, 9 and 10, 1955. Edited by Claude A. Villee, Ph.D. Price, $5. Pp 262, with 118 illustrations. Josiah Macy, Jr. Foundation Publications, 16 W. 46th St., New York 36, 1955.

The Inquisitive Physician: The Life and Times of George Richards Minot, A. B., M. D., D. Sc. By Francis M. Rackemann, A.B., M.D. Price, $5. Pp 288, with illustrations Harvard University Press, 44 Francis Ave. Cambridge 38, Mass., 1956.

Mitral Stenosis. By Knud Henning Olesen. Price, 18.00 k. Pp 228, with 11 illustrations, 77 tables, and 22 charts. **Ejnar** Munksgaards Forlag, Nørregade 6 Copenhagen, 1955.

Derniers Aspects du monde des mycobacteries. By Paul Hauduroy. Price, 750 fr. Pp. 94. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6°, 1955.

Histopathologie du foie. By P. Cazal. Price, paper, 4000 fr.; cloth, 4800 fr. Pp 208 with 213 illustrations (24 in color). Masson & Cie, 120 boulevard Saint-Germain, Paris, 6°, 1955.

Der primaere Leberkrebs. By Kurt Köhn. Price, 15.60 DM. Pp. 89, with 85 illustrations and 3 charts. Springer-Verlag, Reichpietschufer 20, (1) Berlin W. 35, 1955.

Lehrbuch der inneren Medizin. Edited by Ludwig Heilmeyer. Price, 68.00 DM. Pp 1346, with 197 illustrations (44 in color). Springer-Verlag, Reichpietschufer 20, Berlin W. 35, 1955.

Clinical Recognition and Management of Disturbances of Body Fluids. Second Edition. By John H. Bland, M. D. Price, $11.50. Pp 522, with 109 illustrations and 53 tables. W. B. Saunders Company, 218 W. Washington Sq. Philadelphia 5, 1956.

Electrocardiography: Fundamentals and Clinical Application. Second Edition. By Louis Wolff, M.D. Price, $7. Pp 342, with 199 illustrations and 11 tables. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

La Fonction ovarienne et son exploration. By R. Vokaer. Price, 850 fr. Pp 108, with 54 illustrations and many tables. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6°, 1956.

Les Vitamines: Biochimie—biologie—emploi therapeutique. By Henri Thiers, Price, paper, 4000 fr., cloth, 4600 fr. Pp 626, with many charts and tables. Masson & Cie, 120 boulevard Saint-Germain, Paris 6°, 1956

Nauheimer Fortbildungs-Lehrgange: Vol. 21. Interne Therapie der organischen Herz- und Kreislauferkrankungen. Price 13.00 DM. Pp 130, with 26 illustrations and 8 tables. Dr. Dietrich Steinkopf Verlag, Holzhofallee 35, (16) Darmstadt, 1956.

Studies on Fertility 1955, including papers read at the Conference of the Society for the Study of Fertility, Birmingham, 1955. Vol. VII. Edited by R. G. Harrison, M.D., D.M. Price, $5. Pp. 156, profusely illustrated. Blackwell Scientific Publications, 24-25 Broad St., Oxford; Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Police Drugs. By Jean Rolin. Price, $4.75. Pp. 194, with no illustrations. Philosophical Library, 15 E. 40th St., New York 16, 1956.

The Truth About Cancer. By Charles S. Cameron, M.D. Price, $4.95. Pp. 268, with 16 illustrations and 41 plates (13 in color). Prentice-Hall, Inc., 70 Fifth Ave., New York 11, 1956.

Laboratory Tests in Common Use. By Solomon Garb, M.D. Price, $2. Pp. 160, with 6 tables. Springer Publishing Company, 44 E. 23d St., New York 10, 1956.

Textbook of Medical Physiology. By Arthur C. Guyton, M.D. Price, $13.50. Pp. 1030, with 577 illustrations. W. B. Saunders Company, 218 W. Washington Sq. Philadelphia 5, 1956.

Fibrocystic Disease of the Pancreas: Report of the Eighteenth Ross Pediatric Research Conference September 30-October 1, 1955. Edited by Robert G. Frazier, M.D. Price, not given. Pp. 92, with 26 tables and 15 charts. Ross Laboratories, Columbus 16, Ohio, 1956.

In the Doctor's Office: The Art of the Medical Assistant. Second Edition. By Esther Jane Parsons. Price, $3.95. Pp. 326, with 11 figures and several drawings. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

Collagen Diseases Including Systemic Lupus Erythematosus—Polyarteritis—Dermatomyositis—Systemic Scleroderma— Thrombotic Thrombocytopenic Purpura. By John H. Talbott, M.D. and R. Moleres Ferrandis, M.D. Price, $6.50. Pp. 232, with 30 illustrations and 16 color plates. Grune & Stratton, Inc., 381 Fourth Ave., New cork 16, 99 Great Russell St., London, W. C. 1, 1956.

Adrenal Function in Infants and Children. Edited by Lytt T. Gardner, M.D. Price, $6.75. Pp. 221, with many charts and tables. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W. C. 1, 1956.

Pulmonary Carcinoma: Pathogenesis, Diagnosis and Treatment. Edited by Edgar Mayer, M.D., and Herbert C. Maier, M.D. Price, $15. Pp. 540, with approximately 200 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

News and Comment

ANNOUNCEMENTS

Public Health Service Research Grants.—The Public Health Service has announced a new procedure to expedite the processing of research grant applications for those requests which do not exceed $2000 plus indirect costs and which do not ask support for more than one year. Such applications will be accepted and processed on receipt and are not therefore subject to the usual deadlines for submission prior to review.

Council recommendations can be expected on these applications within one to four months from the time of submission. These procedures do not apply for requests for supplements to existing grants.

Address all applications as well as requests for forms or additional information to the Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

IVth International Congress of Internal Medicine.—The IVth International Congress of Internal Medicine is to be held in Madrid, Sept. 19-23, 1956. Details of the program and application for attendance may be obtained by addressing the secretaries, Dr. J. C. de Oya or Dr. J. Gimena, Hortaleza, 90, Madrid.

Nonmembers of the association may attend.

Laboratory Refresher Training Courses.—The following Schedule of Laboratory Refresher Training Courses will be offered by the Laboratory Branch of the Communicable Disease Center, Chamblee, Ga., during the period July, 1956-June, 1957.

Information and application forms should be requested from Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, P.O. Box 185, Chamblee, Ga.

Location of Classrooms: 1—Bldg. 27, Chamblee, Ga.; 2—Bldg. 30, Chamblee, Ga.; 3—Virus Laboratory, Montgomery, Ala.

Dates	Course No.	Courses	Duration	Location
Sept. 10—21	8.40	Laboratory Methods in the Diagnosis of Bacterial Diseases Part 1. General Bacteriology	2 wk.	2
Sept. 10—Oct. 5	8.00	Laboratory Methods in the Diagnosis of Parasitic Diseases Part 1. Intestinal Parasites	4 wk.	1
Sept. 24—Oct. 5	8.41	Laboratory Methods in the Diagnosis of Bacterial Diseases Part 2. General Bacteriology	2 wk.	2
Oct. 8—19	8.50	Laboratory Methods in the Diagnosis of Bacterial Diseases, Enteric Bacteriology	2 wk.	2
Oct. 8—26	8.01	Laboratory Methods in the Diagnosis of Parasitic Diseases Part 2. Blood Parasites	3 wk.	1
Oct. 15—26	8.20	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases	2 wk.	3
Oct. 29—Nov. 2	8.26	Laboratory Methods in the Diagnosis of Rabies	1 wk.	3

Jan. 7—18	8.15	Laboratory Methods in Medical Mycology Part 1. Cutaneous Pathogenic Fungi	2 wk.	1
Jan. 21—Feb. 1	8.16	Laboratory Methods in Medical Mycology Part 2. Subcutaneous & Systemic Fungi (Completion of Course 8.15 or equivalent education or experience is a prerequisite.)	2 wk.	1
Jan. 21—Feb. 1	8.55	Laboratory Methods in the Diagnosis of Tuberculosis	2 wk.	2
Feb. 4—15	8.17	Laboratory Methods in the Study of Pulmonary Mycoses	2 wk.	1
Feb. 25—March 1	9.40	Laboratory Diagnostic Methods in Veterinary Mycology	1 wk.	1
March 11—22	8.20	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases	2 wk.	3
March 11—22	9.41	Serologic Methods in the Diagnosis of Parasitic and Mycotic Infections	2 wk.	1
March 25—29	8.26	Laboratory Methods in the Diagnosis of Rabies	1 wk.	3

The following courses are given by special arrangement only.

8.05	Laboratory Methods in the Diagnosis of Malaria	2 wk.	1
8.21	Virus Isolation and Identification Techniques	2-4 wk.	3
8.42	Typing of Corynebacterium diphtheriae	1 wk.	2
8.51	Special Problems in Enteric Bacteriology	2 wk.	2
8.52	Phage Typing of Salmonella typhosa	1 wk.	2
8.53	Laboratory Methods in the Diagnosis of Leptospirosis	1-4 wk.	2
8.54	Serologic Differentiation of Streptococci	2 wk.	2

American College of Physicians.—The American College of Physicians held its Thirty-Seventh Annual Session at Los Angeles, Calif., April 16-20, 1956, with a gross registration of over 4500. Dr. Walter L. Palmer, of Chicago, was inducted as President. Other officers elected were Dr. Richard A. Kern, Philadelphia, President-Elect; Dr. Chester M. Jones, Boston, First Vice-President; Dr. George H. Anderson, Spokane, Wash., Second Vice-President; Dr. Truman G. Schnabel Sr., Philadelphia, Third Vice-President; Dr. Wallace M. Yater, Washington, D. C., Secretary-General. Dr. William D. Stroud, Philadelphia, was re-elected Treasurer.

The 1957 Annual Session will be held at Boston, April 8-12; the 1958 Annual Session will be held at Atlantic City N. J., April 28-May 2.

Third Ibero Latin American Congress of Dermatology.—The Third Ibero Latin American Congress of Dermatology will be held in Mexico City from Oct. 21 to 27, 1956.

For details, write to Dr. Manuel Malacara, Secretary, Centro Dermatológico Pascua, Calle Dr. Garciadiego 21, México 7, D. F.

Course in Postgraduate Gastroenterology.—The American College of Gastroenterology announces that its Annual Course in Postgraduate Gastroenterology will be given at The Roosevelt, in New York City, on Oct. 18, 19, and 20, 1956.

The course will again be under the direction and co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School, who will serve as surgical coordinator, and Dr. I. Snapper, Director of Medical Education, Beth-El Hospital, Brooklyn, who will serve as medical coordinator. Drs. Wangensteen and Snapper will be assisted by a distinguished faculty selected from the medical schools.

The subject matter to be covered in the course, from a medical as well as surgical viewpoint, will cover, essentially, the advances in diagnosis and treatment of gastrointestinal diseases and a comprehensive discussion of diseases of the mouth, esophagus, stomach, pancreas, spleen, liver and gall bladder, colon, and rectum, with special studies of radiology and gastroscopy.

For further information and enrollment write to the American College of Gastroenterology, Department P.G., 33 W. 60th St., New York 23.

First Inter-American Conference on Occupational Medicine and Toxicology.—The University of Miami, School of Medicine, jointly with the University of Havana, School of Medicine, Cuba, will hold this year the first inter-American Conference on Occupational Medicine and Toxicology. The meeting will be held Sept. 3 to 7. The official language of the program will be Spanish.

This year the conference will be held in Miami, with the University of Miami, School of Medicine, serving as host. It is expected that this conference will be repeated next year, with the University of Havana serving as host.

The program is in the hands of a committee from these two universities. General Chairman of this year's meeting is Dr. Homer F. Marsh, Dean of the School of Medicine of the University of Miami. Co-chairmen for the University of Miami include Dr. Ralph Jones Jr., Professor of Medicine, Dr. Willard Machle, Research Associate Professor of Pharmacology, and Dr. William B. Deichmann, Professor of Pharmacology. The committee of the University of Havana includes Dr. Angel Perez André, Acting Dean (Vice-Dean), Dr. Rafael Penalver, Instructor in Legal Medicine and Toxicology, Dr. Vincente Pardo Castello, Assistant Professor of Dermatology, and Dr. Francisco Lancis y Sanchez, Assistant Professor of Legal Medicine and Toxicology.

The program at this time includes speakers from Venezuela, Mexico, Peru, Colombia, Chile, Puerto Rico, Cuba, and the United States.

Papers to be presented include topics such as the following: establishment of a "Medical Department in Industry," "Work and Fatigue in Industry," "Effects of Environmental Conditions on the Health of the Occupational Worker," "Recording of Medical Case Histories," "Control of Malaria in Endemic Areas," "Occupation and Heart Disease," "The Role of the Anesthesiologist in Acute Poisonings," "Neurological Problems in Occupational Medicine and Toxicology," "The Treatment of Intoxications by Organic Phosphates," "Management of Berylliosis," "Treatment of Manganese Intoxication."

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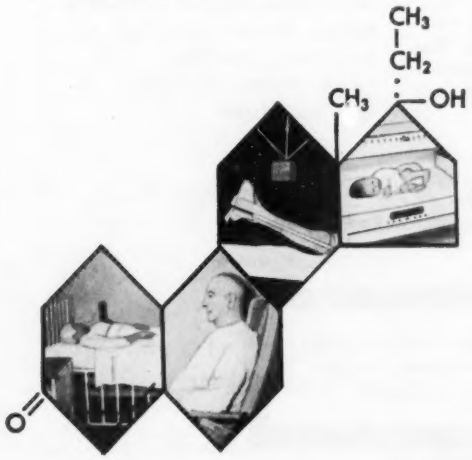

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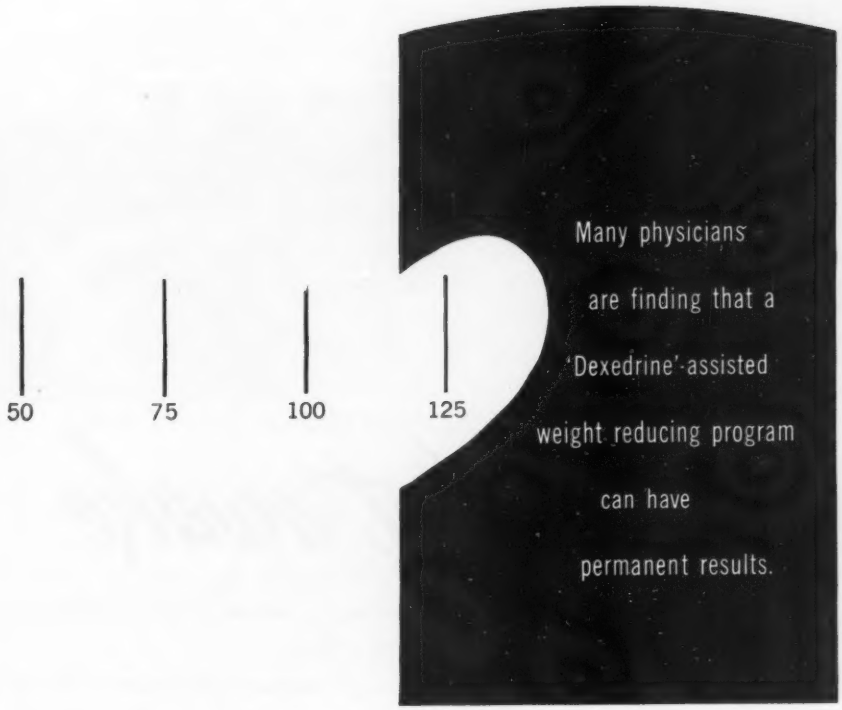

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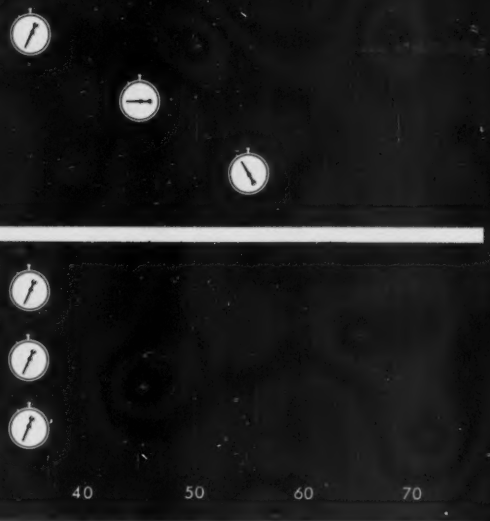

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*T.M. Reg. U.S. Pat. Off.